Environmentally Benign Acylation Reactions

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Finally I wish to thank my entire family for not giving up on me and for believing that I could complete this. I am extremely grateful to my Gran for her support with my MRes studies that led to me commencing this PhD, without her help I would not be writing this. I also wish to thank my brother Nick for his continued advice and support. Thank you to my parents who have not stopped supporting me in my studies, it has meant a great deal to me.

My biggest thank you is to my wife who has tirelessly put up with all of the stresses and strains of the past four years and supported me throughout without question. It is through her strength that I have been able to achieve this, thank you. During the writing of this thesis I became a father, Charlotte Jessica Wakeham was born on the 31st December 2013. I hope that this makes her proud because she has changed my life forever, for the better.

Abbreviations

Act	Activation
ATH	Asymmetric transfer hydrogenation
Bn	Benzyl
***t*Bu**	Tertiary butyl
***n*Bu**	Butyl
Cat	Catalytic
$CDCl_3$	Deuterated chloroform
CDI	Carbonyldiimidazole
CMPI	2-Chloro-1-methyl-pyridinium iodide
COD	*cis*, *cis*-1,5-Cyclooctadiene
Cp^*	Pentamethylcylcopentadienyl
δ	Chemical shift
DBN	1,5-Diazabicyclo[4.3.0]non-5-ene
DCC	*N,N*'-Dicyclohexylcarbodiimide
DCM	Dichloromethane
DMA	Dimethylacetamide
DMAP	4-Dimethylaminopyridine
dme	Dimethoxyethane
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
DPEPhos	(Oxydi-2,1-phenylene)bis(diphenylphosphine)
dppb	1,4-Bis(diphenylphosphino)butane
d*t*bpy	4,4'-Di-*tert*-butyl-2,2'-dipyridyl
EDC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
EDG	Electron donating group
eq.	Equivalent
esp	*α,α,α',α'*,-Tetramethyl-1,3-benzenedipropionate
Et_3N	Triethylamine
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
EtOH	Ethanol

i	Iso
IPA	Isopropanol
IPAC	Isopropyl acetate
J	Coupling constant
MeCN	Acetonitrile
MS	Molecular Sieves
NaOEt	Sodium ethoxide
NBS	*N*-Bromosuccinimide
NMR	Nuclear Magnetic Resonance
Nuc	Nucleophile
p	Para
Ph	Phenyl
PhMe	Toluene
PNN	2-((Di-*tert*-butylphosphinomethyl)-6-diethylaminomethyl)pyridine
PyBOX	Pyridine linked bisoxazoline ligand
R	Unspecified generic group
r.t.	Room temperature
t	Tertiary
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Tetramethylsilane
tRNA	Transfer Ribonucleic Acid
TsCYDN	*N*-(1,2-Diaminocyclohexane)-*p*-toluenesulfonamide
TsDpen	*N*-(2-Amino-1,2-diphenylehtyl)-*p*-toluenesulfonamide
TTP	Tetrakis(*p*-tolyl)porphyrin

Abstract

This thesis outlines the work carried out in the last three and half years concerning the development of environmentally benign acylation reactions and determination of the range of these reactions through substrate screening and investigations into the mechanisms by which they are operating.

Chapter 1 aims to introduce homogeneous catalysis as an important area of chemical research, subsequently focusing of sulfonamides and in particular the *N*-acylation of sulfonamides and the current procedures that are available in the literature. The introduction also covers transfer hydrogenation reactions and how this can be applied to acylation reactions. Finally the introduction shows how asymmetric transfer hydrogenation is currently performed.

Chapter 2 investigates using iodide as an activating agent for acid chlorides in the acylation of various substrates; mechanistic information was determined through NMR studies.

Chapter 3 details work investigating alternative hydrogen sources for asymmetric transfer hydrogenation and the use of existing catalysts in conjunction with a novel hydrogen source.

Chapter 4 shows work investigating the possibility of using alcohol as an acylating agent for sulfonamides using transfer hydrogenation catalysts.

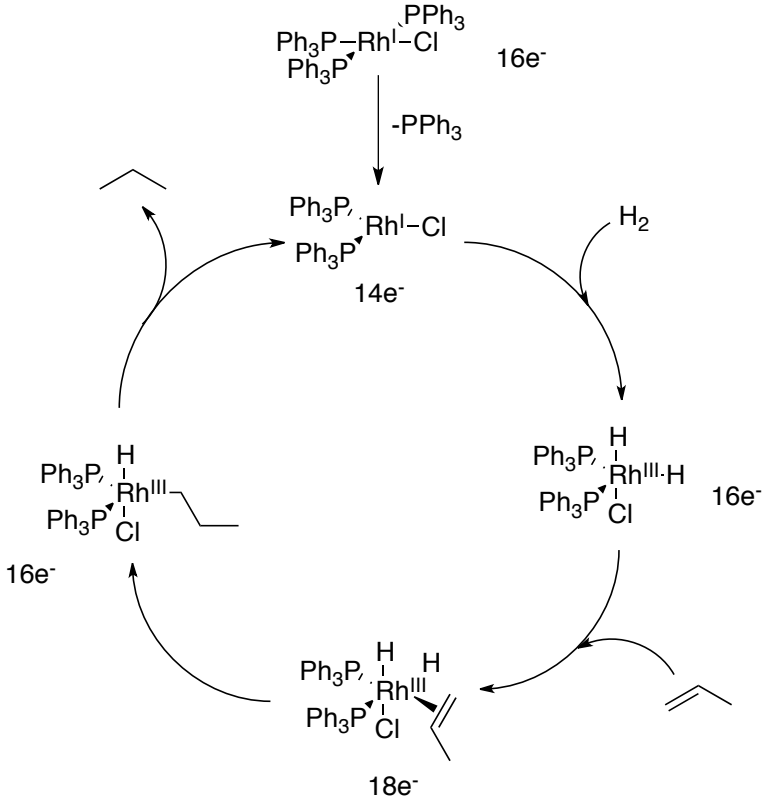
Chapter 1: Introduction

1.1 Homogeneous Catalysis

Homogeneous catalysis is one of the most important areas of current chemical research.[1] A homogeneous catalyst is a catalyst in the same phase as the components of the reaction that it is catalysing. This is in contrast to heterogeneous catalysts which are catalysts in a different phase from the components of the reaction.[2] This introduction to homogenous catalysis will show examples of industrial and fine chemical uses in order to display the variety of uses that this type of catalysis has and also its continued importance in modern organic chemistry.

1.1.1 Industrial Importance

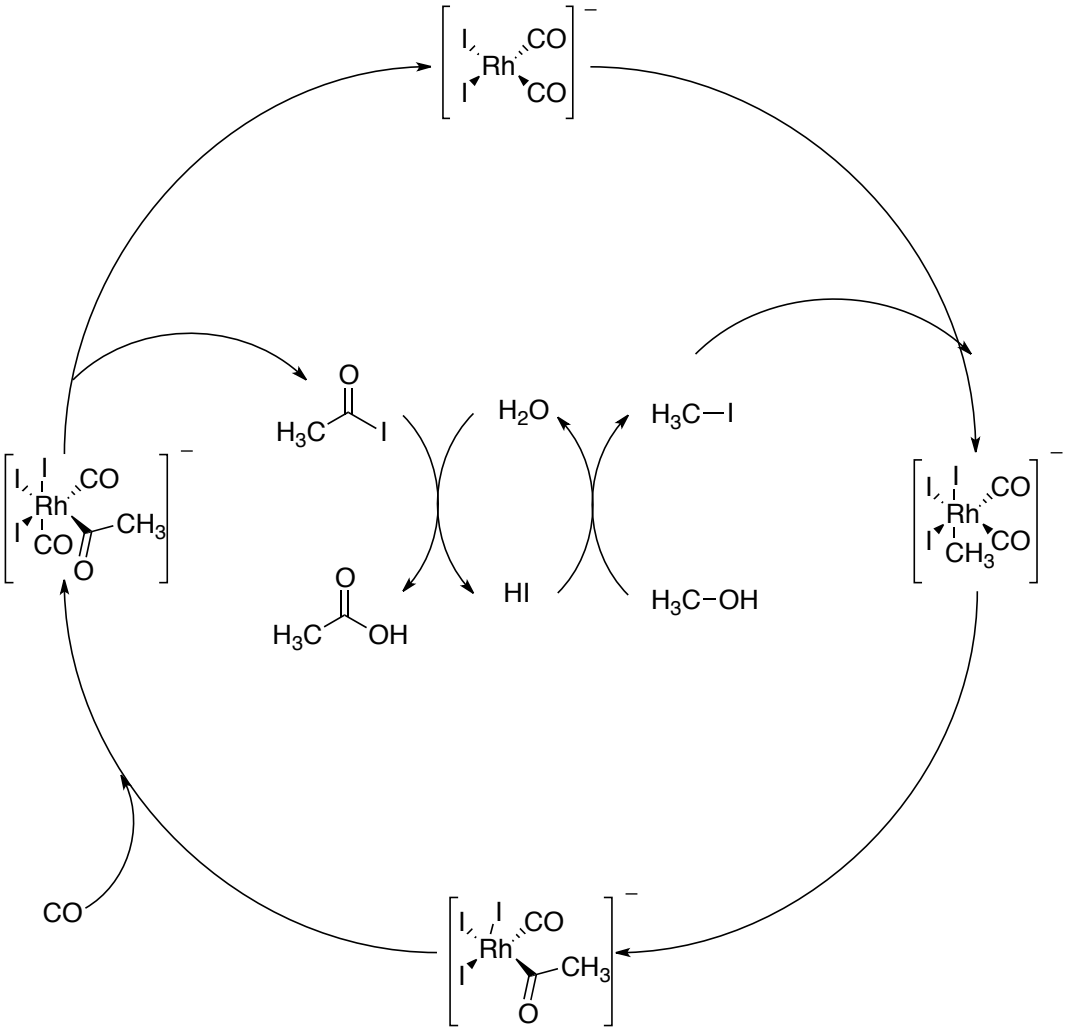
Homogeneous catalysis is extremely important in industrial processes. The following are examples of some of the most important. Scheme 1.1 shows Wilkinson's catalyst, widely used for the hydrogenation of alkenes at room temperature and under 1 bar H_2.[3]



Scheme 1.1

The process relies on the oxidative addition of hydrogen to a rhodium catalyst. This yields an octahedral complex that dissociates giving a coordinatively unsaturated 16 electron species. The alkene can associate to this species and the reductive elimination step occurs to yield the saturated alkane.

The next example is the conversion of methanol to acetic acid, this process is carried out on ~3.5 Mt scale, per year, worldwide, it is called the Monsanto process.[4] The catalytic cycle is shown in Scheme 1.2.

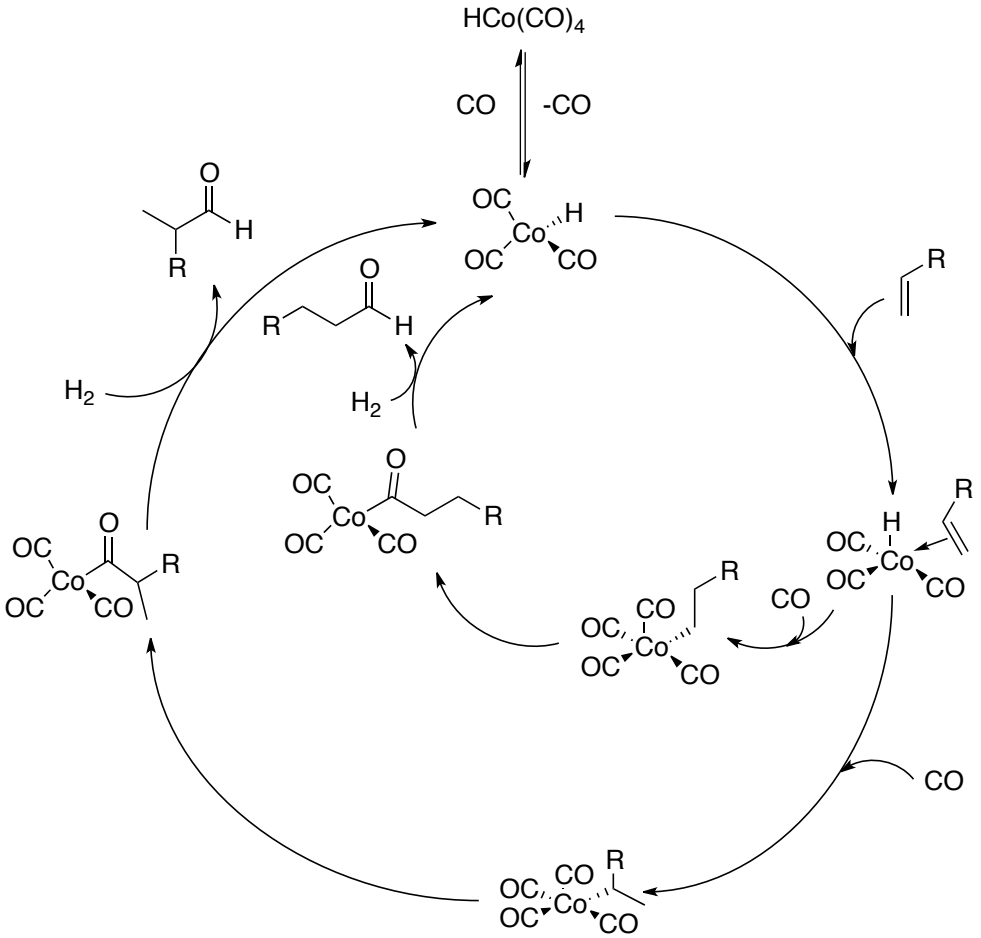


Scheme 1.2

The key steps in this process are nucleophilic substitution on methanol, the oxidative addition of methyl iodide to the rhodium catalyst and reductive elimination of acetyl iodide, which readily hydrolyses to acetic acid.

The Monsanto process also inspired the Tennessee-Eastman acetic anhydride process, which relies on a very similar catalytic cycle where lithium iodide replaces hydroiodic acid and methyl acetate replaces methanol, with anhydride as the product.[5]

One of the oldest examples of homogeneous catalysis in an industrial process, that is still relevant, is Hydroformylation, sometimes referred to as the Oxo-process. Hydroformylation is the conversion of alkenes to aldehydes using carbon monoxide and hydrogen gases, catalysed by rhodium or cobalt catalysts.[6]



Scheme 1.3

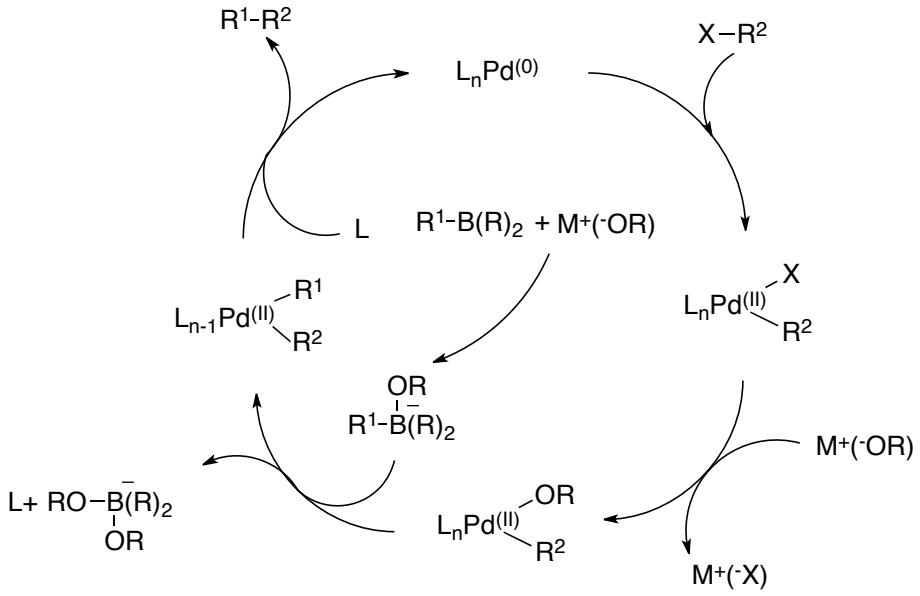
These industrial examples are not exhaustive; there are an extensive number of homogeneous catalysts employed in both fine and bulk chemical synthesis. Another

major example, that will not be covered in detail here is the Shell Higher Olefins Process (SHOP), which uses a nickel based catalyst to oligomerize ethene.[7]

1.1.2 Fine Chemical Synthesis

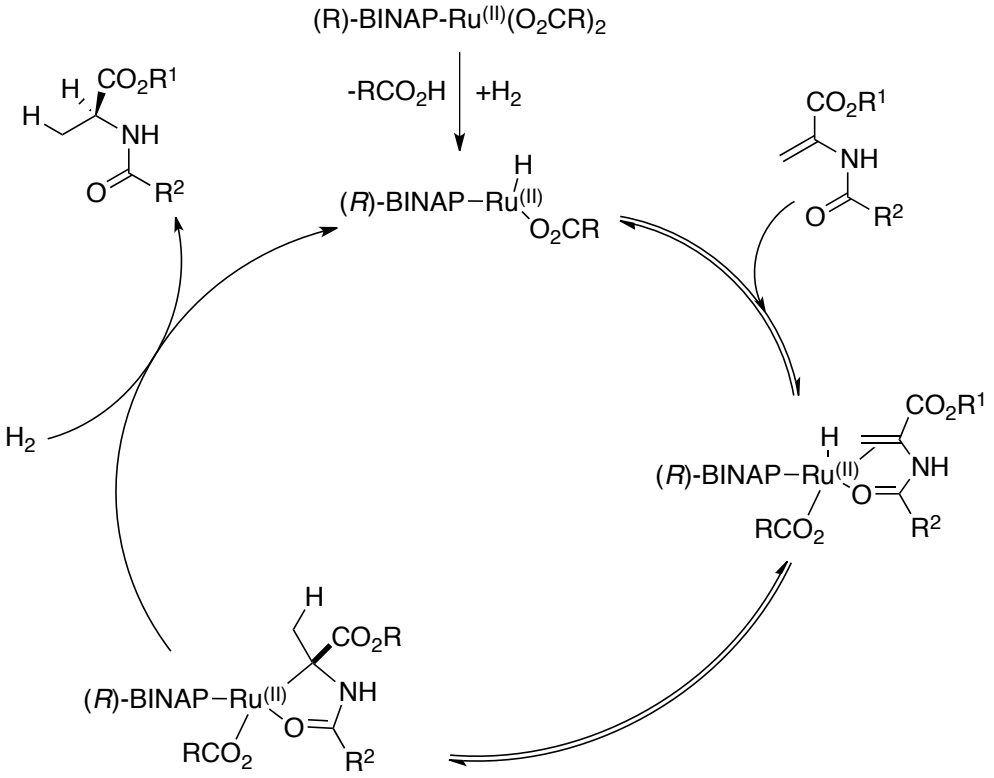
The previously discussed industrial examples of homogeneous catalysis are employed on a vast scale. There are however, significant disadvantages to the large-scale use of homogeneous catalysts. These include: the cost of catalyst precursors owing to the expense of precious metals used; asymmetric syntheses often rely on chiral ligands and these are usually only available in small quantities; separation and recovery of the catalyst from the product solution is perhaps the largest issue. However, in fine chemical synthesis the large-scale issues are less of an obstacle and in this section of the introduction the aim is to show examples of the most relevant homogeneous catalysts.

Cross-coupling reactions are among the most widely used and researched reactions in modern chemistry. The Nobel Prize was awarded to *Suzuki et al.* in 2010 for their pioneering work in this area.[8]



Scheme 1.4

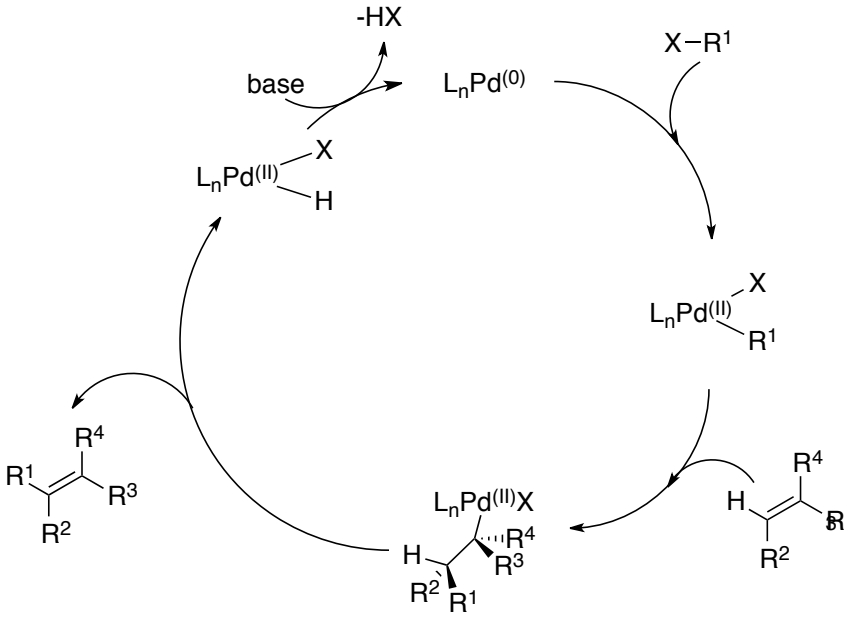
Scheme 1.4 shows the typical *Suzuki* cross coupling reaction, an excellent example of homogeneous catalysis. Oxidative addition followed by metathesis, transmetallation and finally reductive elimination to give the cross-coupled product.



Scheme 1.5

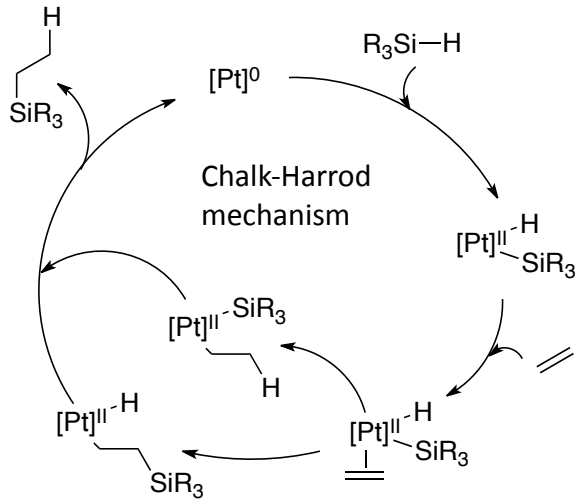
Noyori won the Nobel Prize with others for their work on asymmetric hydrogenation, the general scheme is shown in Scheme 1.5. It involves catalytic hydrogenation using a chiral ruthenium catalyst under high-pressure hydrogen gas to hydrogenate various olefins in a chiral manner.[9]

The Heck reaction is another classic example of homogeneous catalysis that is enormously important for organic chemists. It is a cross-coupling reaction between aryl, benzyl or styryl halides and olefins to form the corresponding substituted olefins. The catalytic cycle is shown in Scheme 1.6 and demonstrates the process.[10]



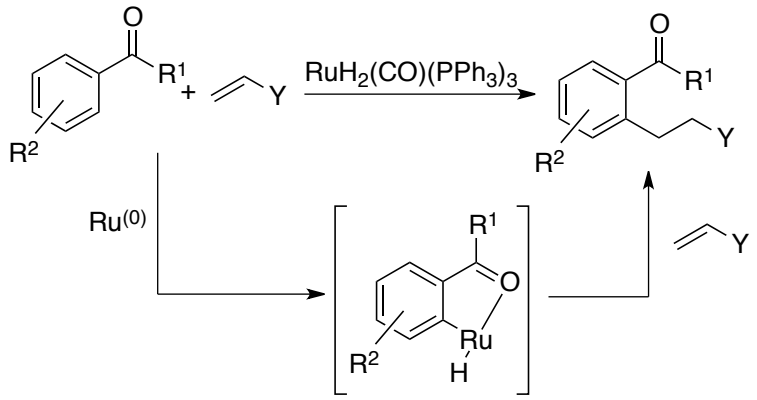
Scheme 1.6

Hydrosilation, or catalytic hydrosilation is the addition of a Si-H bond across an unsaturated C-C bond.[11] According to *Ullmann's* encyclopedia of industrial chemistry, hydrosilation is the most important application of platinum in homogeneous catalysis.[12] The widely accepted mechanism for hydrosilation is called the Chalk-Harrod mechanism,[13] industrially hydrosilyation is often carried out using Speier's catalyst, H_2PtCl_6.[14]



Scheme 1.7

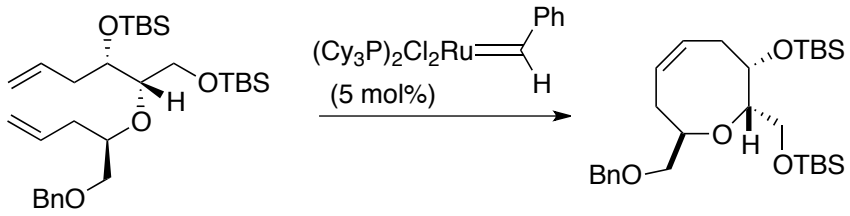
C-H functionalization is a reaction that cleaves a carbon-hydrogen bond. The carbon-hydrogen bond is a particularly strong bond and is stable towards many reagents, with the exception of some reactive oxygen compounds. Functionalization requires activation of a C-H bond, one of the earliest catalytic example of this type of activation uses a ruthenium catalyst and is shown below in Scheme 1.8.[15]



Scheme 1.8

The ketone is *ortho* directing for C-H activation and alkylation of aryl systems like this can be achieved. Many advances have been made in the field of C-H activation and it remains one of the great challenges facing chemists.

The final example in this short introduction to homogeneous catalysis is Grubbs catalyst, which performs olefin ring-closing metathesis, shown in Scheme 1.9.[16]



Scheme 1.9[17]

The examples of industrial and fine chemical applications of homogeneous catalysis show the power and relevance of this type of catalysis to organic chemists. This thesis focuses on three different types of homogeneous catalysis and it was considered prudent to give an overview of the area of chemistry. The following sections of the introduction will address the three specific areas individually in much more detail.

1.2 Activation of acid chlorides for acylation reactions

The first area of homogeneous catalysis focused on in this introduction is the catalytic activation of acid chlorides with a view to performing *N*-acylation of a sulfonamide.

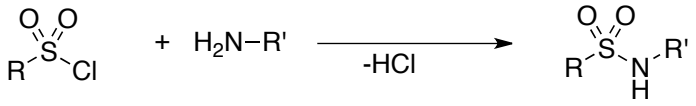
1.2.1 Sulfonamide

Since the focus of this thesis is on the acylation of a sulfonamide it is worth considering the basic chemistry of a sulfonamide. Please note however, that as will be discussed in Chapter 2, investigations were also made into the acylation of other poor nucleophiles.

Scheme 1.10

The sulfonamide functional group is analogous to the amide functional group. The lone pair of electrons on nitrogen in both functional groups can donate into the π* orbital on the adjacent atom, in the case of an amide the π* orbital of the (C=O) carbonyl carbon and in the sulfonamide the π* orbital of the (O=S=O) sulfonyl sulfur. It is this delocalization of electron density that explains the stability of amides and sulfonamides. The delocalization of the lone pair of electrons also explains the reduced nucleophilicity of the nitrogen, which will be shown to be very important to the work discussed in this thesis.

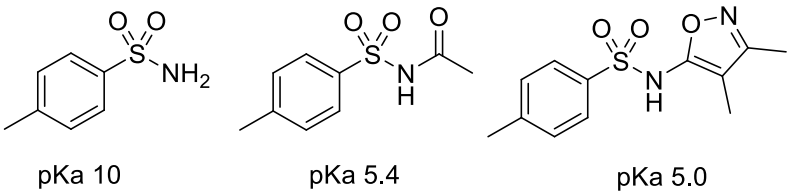
Typically sulfonamides are derived from the reaction of sulfonic acid or sulfonyl chloride derivative with an amine source, as shown in Scheme 1.11.[18]



Scheme 1.11

Interestingly this method is the basis of the Hinsberg test. The Hinsberg test was used to characterize a primary, secondary or tertiary amine. To conduct the test the amine is added to benzenesulfonyl chloride. If no product (precipitate) is formed then the amine is tertiary since no reaction can occur between the two. If the product formed dissolves in aqueous sodium hydroxide then the amine is a primary one because the acidic proton on the nitrogen makes it soluble in aqueous sodium hydroxide. So finally if the product is formed but is insoluble in aqueous sodium hydroxide then the amine is secondary.[19]

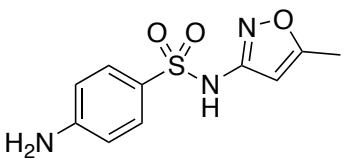
The pKa of a proton on the nitrogen is significantly affected by the electron withdrawing or donating properties of the other substituent on the nitrogen. Scheme 1.12 shows this substituent effect.



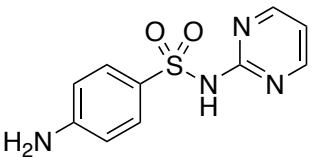
Scheme 1.12

A large portion of research into pharmaceuticals focuses on surrogate functional groups that can be used,[20] for example β-amino acids and the peptides derived from them.[21] In the same way sulfonamides are investigated for their biological activity and potential therapeutic benefits.[22]

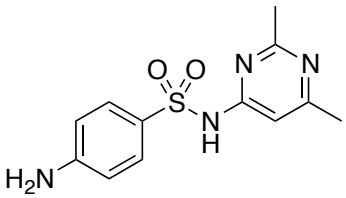
Antibacterial drugs



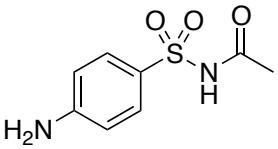
Sulfamethoxazole



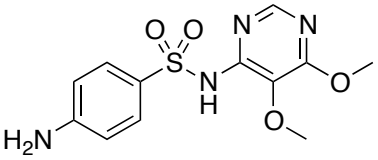
Sulfadiazine



Sulfisomidine

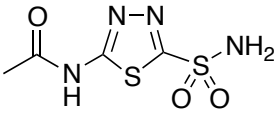


Sulfacetamide

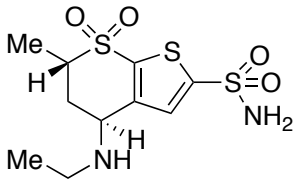


Sulfadoxine

Diuretics

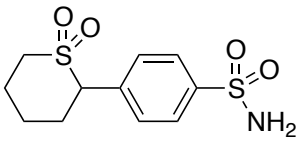


Acetazolamide

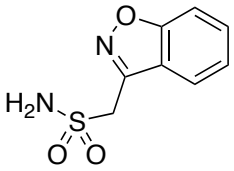


Dorzolamide

Anticonvulsants

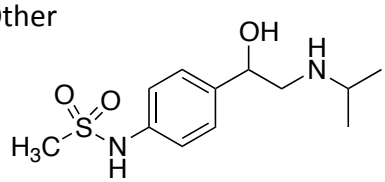


Sultiame

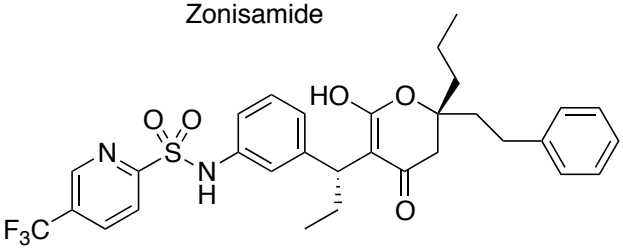


Zonisamide

Other



Sotalol - ß-blocker

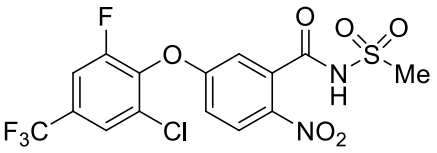


Tipranavir - protein inhibitor

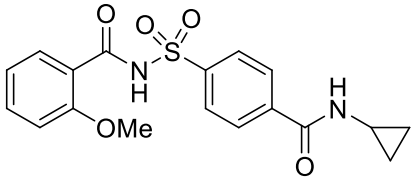
Scheme 1.13

1.2.2 *N*-Acylsulfonamides

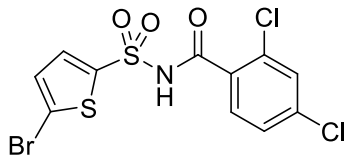
Why investigate acylating sulfonamides? *N*-Acylsulfonamides are an important functional group found in an array of molecules. They have a wide range of applications illustrated by the molecules shown below in Scheme 1.14. Molecules 1 and 2 are herbicides, 3 is an anti-proliferative agent,[23] 4 is a tRNA inhibitor [24] and 5 is an artificial sweetener.[25]



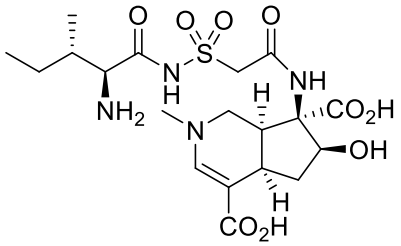
Fomesafen **1**



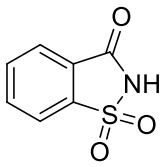
Cyprosulfamide **2**



Anti-proliferative agent LY573636 **3**



tRNA inhibitor SB-203207 **4**



Saccharin **5**

Scheme 1.14

As shown in Scheme 1.12 the *N*-acylsulfonamide moiety has a pKa of approximately 4-5, making the functional group a suitable surrogate for carboxylic acid functional groups. *N*-Acylsulfonamides have been shown to have a variety of therapeutic benefits.[26] Acylsulfonamides are also used as therapeutic agents for Alzeheimer's disease,[27] treatments of osteoporosis,[28] antagonists for angiotensin II[29] and find applications as precursors for a variety of drug molecules, click chemistry intermediates and enzyme inhibitors.[30]

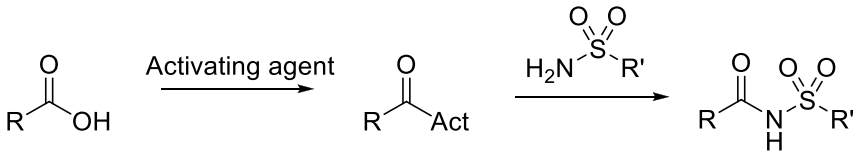
Therefore there is demand for an industrially relevant method that doesn't use toxic catalysts or reagents and that doesn't require a large use of solvents in the purification process. It is also important that the method doesn't produce a large amount of waste by-products, and use relatively mild conditions in the form of ambient temperatures.

1.2.3 Synthesis using coupling agents

The focus of this part of the introduction, Section 1.2, is on the *N*-acylation of sulfonamides and so the examples of coupling agents for the activation of carboxylic acids and acid chlorides shown here reflect that.

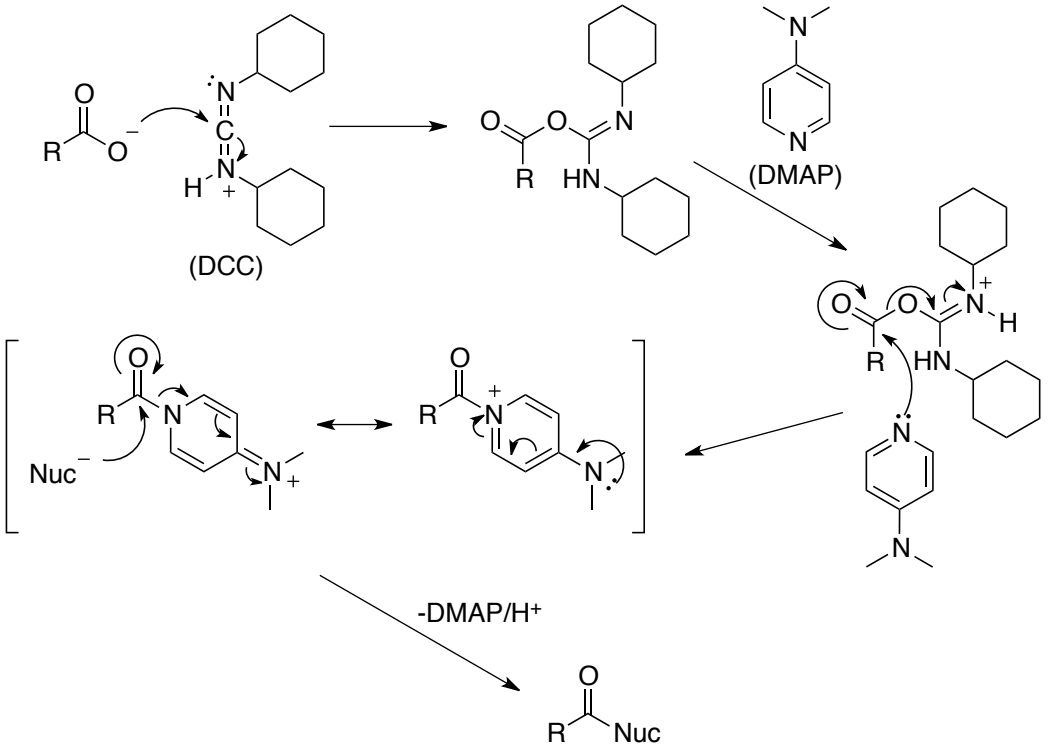
The synthesis of *N*-acetylbenzenesulfonamide was first reported in 1945 and was carried out by addition of acetic anhydride to benzenesulfonamide in the presence of potassium acetate.[31] This was one of the first examples of activating a carbonyl group to make it more susceptible to nucleophilic attack from a sulfonamide.

The alternative approach to their synthesis is to use a base to deprotonate the sulfonamide and therefore generate a stronger nucleophile to attack the carbonyl functional group.



Scheme 1.15

The most common examples of coupling in the literature start with the carboxylic acid and use an activating agent as shown in Scheme 1.15. DMAP and DCC are frequently used in this capacity the mechanism of this reaction is shown below.[32]



Scheme 1.16

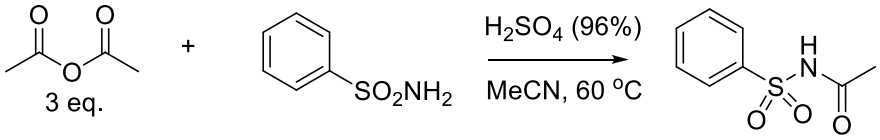
The mechanism shows DCC deprotonating a carboxylic acid, allowing the negative charge on the oxygen to attack the carbodiimide component. This activates the carbonyl making it susceptible to nucleophilic attack from DMAP. This in turn increases the carbonyl susceptibility to nucleophilic attack and the process regenerates DMAP, which can therefore be used in a catalytic amount. This process does, unfortunately generate an equivalent of urea product that requires removal.

EDC.HCl has also been used as a coupling agent in a manner similar to DCC, with one equivalent of DMAP rather than a catalytic amount. EDC.HCL was used mainly because it is water-soluble and therefore this is beneficial in the synthesis of acylsulfonamides for biological applications, the reported yields were not as impressive as with DCC.[28, 33]

Other reagents such as CDI have been used to activate carboxylic acids, this procedure has become known as the, 'Drummond protocol,' for synthesizing *N*-acylsulfonamides.[34] In 1988 Drummond was investigating pharmacologically active

amino acid analogues and reasoned that the *N*-acylsulfonamide group would be of interest to synthesize. The synthesis involves the use of CDI in THF at reflux to activate the carboxylic acid followed by the addition of a sulfonamide.

In 1980 another method was reported which coupled an acid anhydride and a sulfonamide under acidic conditions to afford the *N*-acyl product.[35] This work didn't receive any further attention until 2003 when Martin *et al.* investigated the potential of the acid-catalysed addition of acid anhydride to sulfonamide to afford the corresponding *N*-acylsulfonamide.[36]



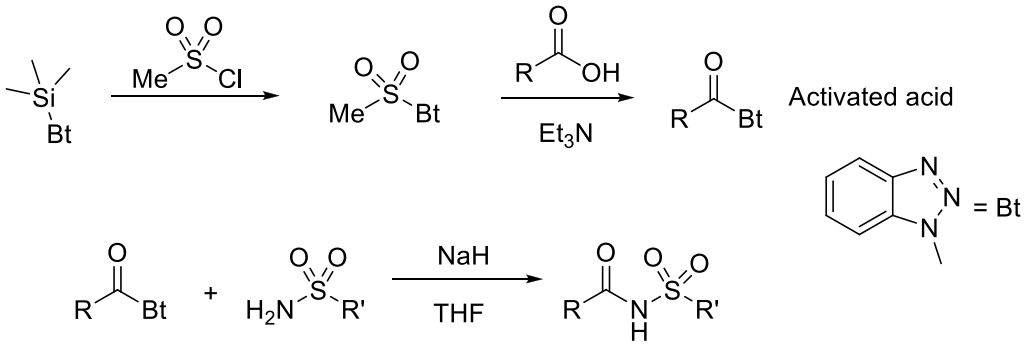
Scheme 1.17[36]

As shown in Scheme 1.17 a large excess (three equivalents) of acid anhydride was used, however the isolated yields for the product shown above and other similar aromatic sulfonamide derivatives were in excess of 90%. The major limitation of the method is the lack of diversity of acid anhydride substrates that produced good yields. For example when benzoic anhydride was coupled to benzenesulfonamide a yield of only 44% was achieved. Furthermore when the anhydride has electron withdrawing or electron donating groups on the phenyl ring no acylation occurred. However, the steric bulk and electronic properties of the sulfonamide were seen to have little effect on isolated yields.

There are two other examples of acid catalysed *N*-acylations of sulfonamides, one is covered in the Lewis acid activated reactions in Section 1.2.3, the other is a method developed by Massah *et al.* in 2008, who used a modified silica support to couple acid anhydrides and acid chlorides to sulfonamides via the acylium intermediate.[37] The procedure involves the reaction of thionyl chloride with silica, over 48 hours, at 120 ˚C, followed by addition of the sulfonamide and either the acid anhydride or acid chloride. The major drawback of this procedure is the two-day preparation time of

the silica gel support and the large waste of silica chloride that is synthesized and then filtered off from the reaction mixture.

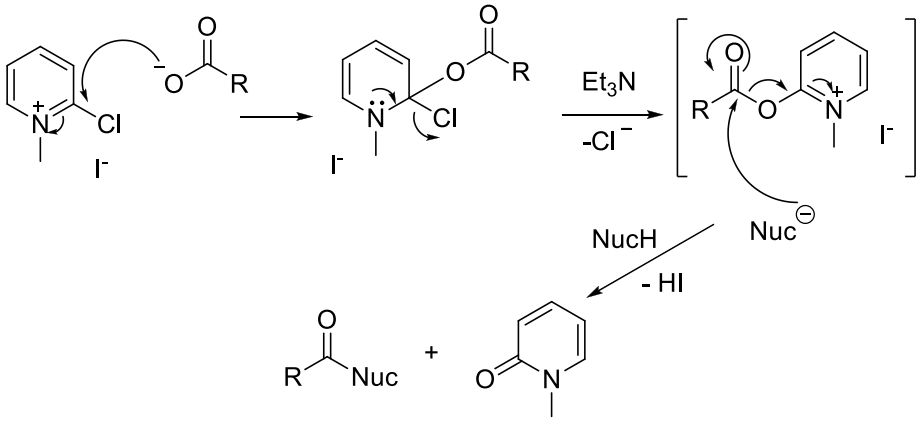
In 2004 Katritzky *et al*. published work showing that *N*-acylbenzotriazones could be used to acylate a wide range of sulfonamides. Scheme 1.18 below shows the method of acylation.[38]



Scheme 1.18[38-39]

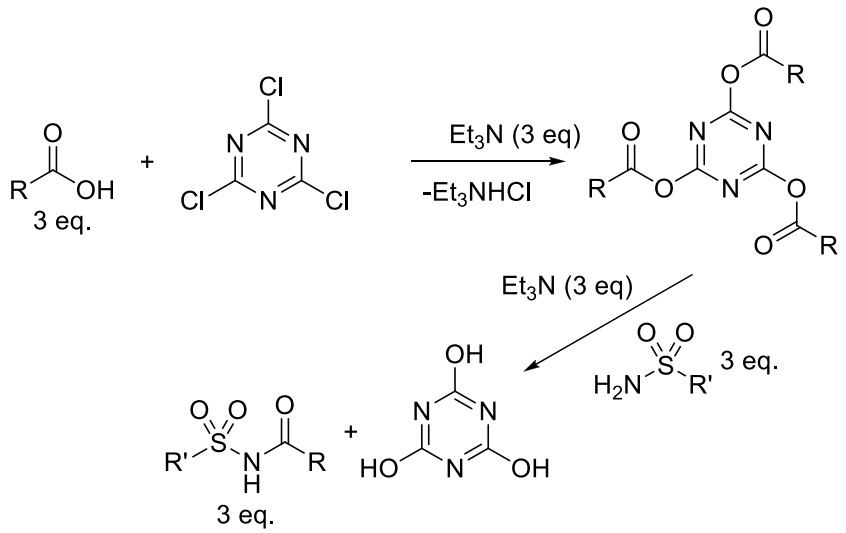
This reaction produces isolated yields of 74-98%, which is excellent. However, the drawbacks of this reaction are clear from the scheme. Firstly, the *N*-acylbenzotriazone has to be synthesised and this takes two steps. The second problem is the acylation of the sulfonamide step takes 24 hours with simple unhindered sulfonamides and takes many days for sulfonamides with sterically or electronically demanding R-groups.

2-Chloro-1-methyl-pyridinium iodide, CMPI, also known as Mukaiyama's reagent, has been shown to activate carboxylic acids for a wide variety of acylations.[40] The mechanism for the reaction was proposed in 1976 and is shown in Scheme 1.19**.**[41]



Scheme 1.19

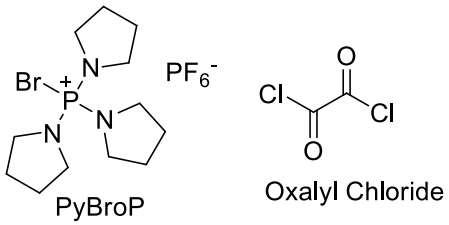
All of the coupling methods have had one problem in common. The problem was that they all produce a stoichiometric amount of waste that has to be removed from the reaction. With that in mind, another coupling agent that has more recently been investigated is cyanuric chloride the mechanism for the reaction is shown in Scheme 1.20 below.



Scheme 1.20

The carboxylic acid was activated and subsequently used to acylate the sulfonamide by improving its electrophilicity. In this instance the cyanuric chloride can activate three equivalents of carboxylic acid this generates three equivalents of HCl and Et_3N is used to remove the HCl.[42] This method produced one third of the amount of waste of activating agent for the product.

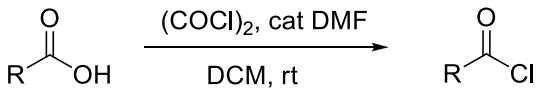
Another way to approach the activation of carboxylic acids was to convert them into the corresponding acid halides and subsequently use them to acylate sulfonamides. The following reagents have been used in this capacity.



Scheme 1.21

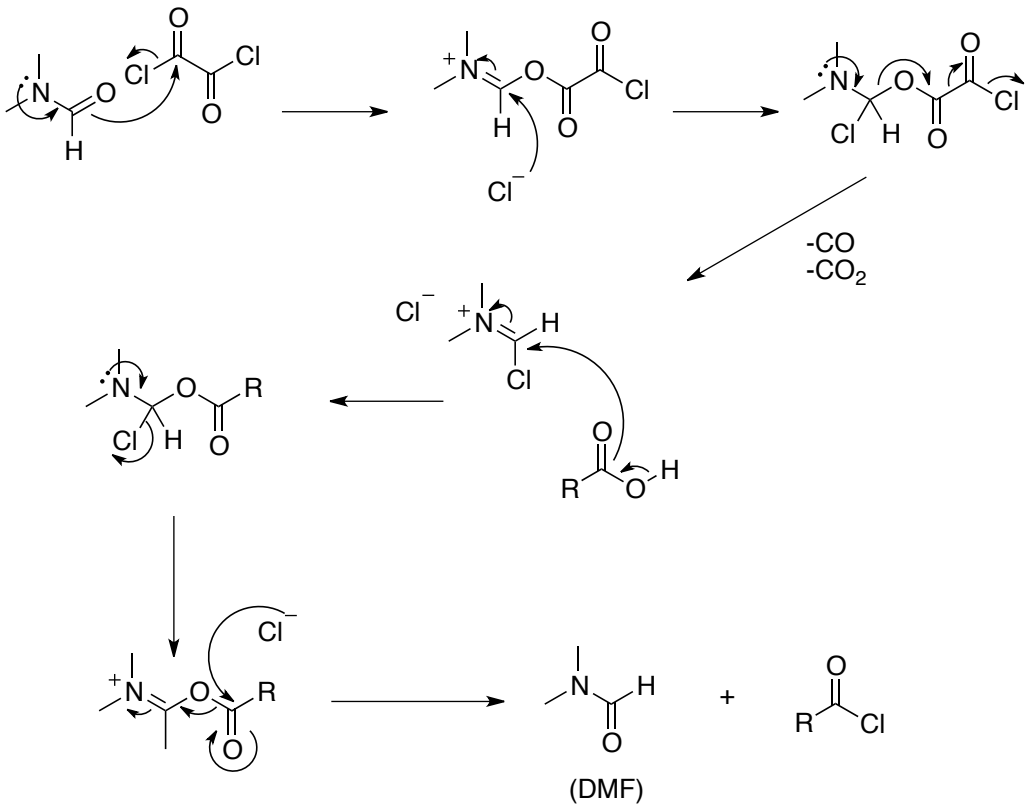
PyBroP is a coupling agent specifically designed to generate an acid halide, it was originally conceived to acylate amines to form amides and there are other analogues that have also been exploited for this coupling.[43] However, with respect to acylating sulfonamides there are two notable examples involving this reagent. The first is synthesis of safety linkers in the acylation of polymer bound sulfonamides, PyBroP was shown to acylate successfully but produced a racemic mixture.[30c] The second example also used in the acylation of polymer bound sulfonamides, finds an application in the treatment of pancreatic disorders. However, PyBroP was not the most efficient reagent and in fact DCC and DMAP combination was shown to acylate more readily.[29b]

Oxalyl chloride is another reagent used to generate the acid chloride to acylate the sulfonamide.



Scheme 1.22

Scheme 1.22 shows the need for catalytic DMF to activate the oxalyl chloride, the mechanism is shown below in Scheme 1.23.



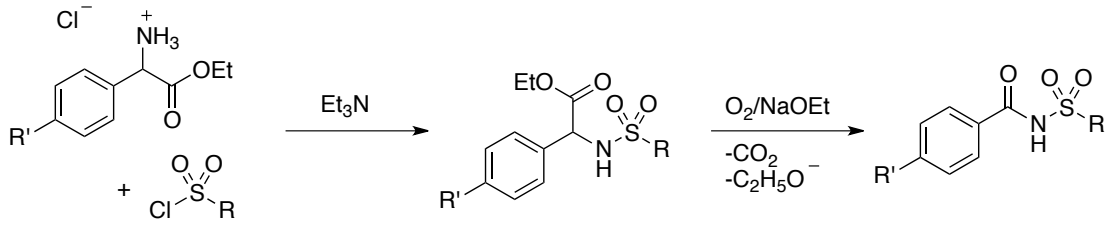
Scheme 1.23[44]

Scheme 1.23 shows that DMF is regenerated in the mechanism hence it can be used in a catalytic amount. The active intermediate is formed by the attack of DMF on the oxalyl chloride, it is this intermediate that is responsible for the acid chloride formation from the carboxylic acid.[44]

Work carried out by Ishusuka *et al*.[45] used this method of acid chloride formation to acylate sulfonamides. The group took a variety of acid chlorides and screened a range of inorganic bases to determine the best method to retain chirality of a starting carboxylic acid through to the chiral *N*-acylsulfonamide product. Powdered KOH, NaOH and LiOH all gave similarly impressive enantioselectivity and isolated yields (>95%, >90%, respectively).

Another method historically employed is the addition of NaH in THF to a sulfonamide to deprotonate the sulfonamide followed by addition of an excess of acid chloride.[46]

The final method in this coupling section approaches the challenge of synthesizing *N*-acylsulfonamides from a different angle, the reaction is shown in Scheme 1.24.[47]



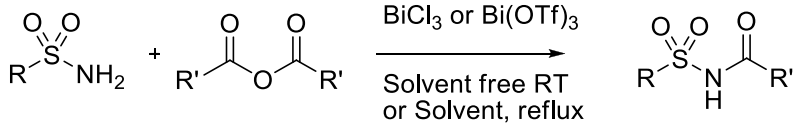
Scheme 1.24

Scheme 1.24 above shows that sulfonyl chlorides can be used to produce alkylated secondary sulfonamides, which are subsequently oxidized with oxygen and sodium ethoxide.

In summary, there are drawbacks to existing coupling reagents, which often produce a stoichiometric amount of waste products that have to be removed from the reaction.

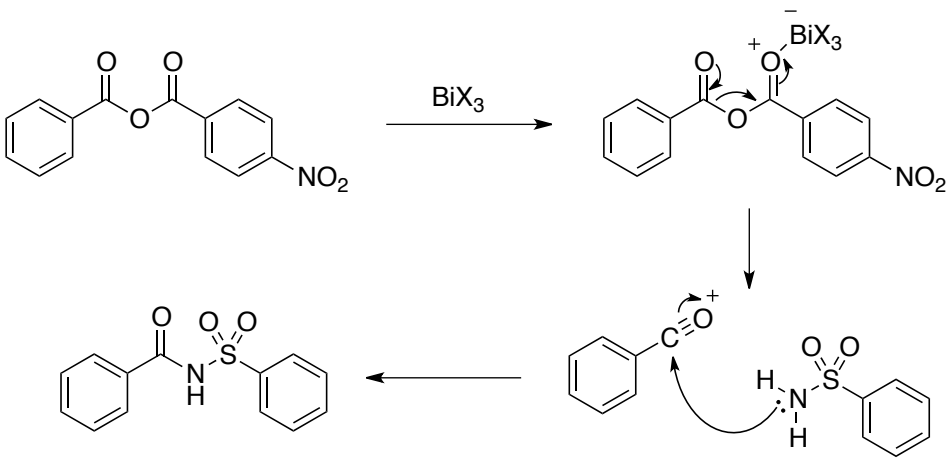
1.2.3 Synthesis using Lewis acid activation

Bismuth(III) has been investigated as a potential catalyst for the *N*-acylation of sulfonamides.[48] Massah *et al.* reported that bismuth(III) chloride and bismuth(III) triflate both showed catalytic activity for the acylations.



Scheme 1.25

The proposed mechanism is shown in Scheme 1.26, the group proposed that the acylium ion is formed and that it was this that undergoes nucleophilic attack from the lone pair on the nitrogen of the sulfonamide.

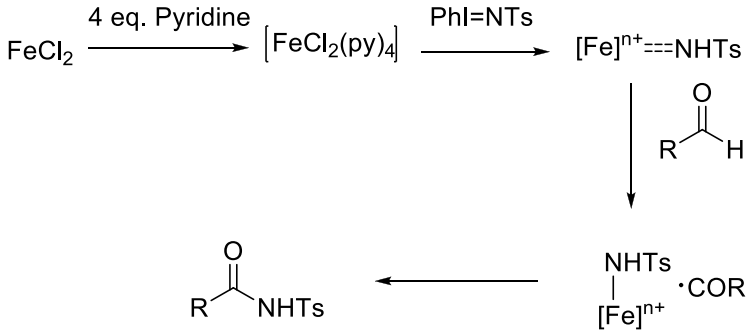


Scheme 1.26

The evidence for the mechanism is provided by the lack of the nitro-substituted product, indicating that the acylium intermediate is formed and made unfavourable with a strongly electron withdrawing group present on the aromatic ring. The bismuth(III) acts as a Lewis acid in this reaction and it is this that leads on to the next development in acylations.

Fu *et al*. published a paper detailing a screening of possible Lewis acids for the *N*-acylation of sulfonamides with carboxylic esters.[49] Titanium(IV) chloride was the most active Lewis acid. However, when 1.5 equivalents were used the test reaction only produced an isolated yield of 53%. Other Lewis acids showed no reaction so the group investigated further and showed that sulfonamides could be acylated and isolated yields for various substrates ranged from 34-76%. Although the yields are not as high as other methods this procedure does have the advantage of starting from the relatively cheap and easy to use carboxylic ester.

Recently Ton *et al.* reported an iron catalysed acylation of sulfonamides.[50] Shown below in Scheme 1.27 is the general reaction pathway for this transformation. Iron(II) chloride reacts with pyridine to form the catalyst *in situ*. The iron complex then activates an aldehyde and then reacts with *N*-tosyliminoiodinane to form the corresponding acylsulfonamide, this type of mechanism will be discussed in further detail in the following section.



Scheme 1.27

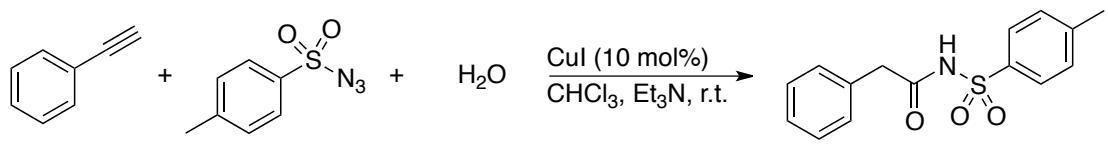
1.3 Transfer hydrogenation

Transfer hydrogenation is the second area of homogeneous catalysis that will be discussed as part of this thesis. The focus of the work described in this thesis was again the acylation of a sulfonamide, however, using alcohols as the acylating agent with catalytic transfer hydrogenation. Here, therefore, other metal catalysed methods for acylating sulfonamides are considered, before considering existing transfer hydrogenation reactions that would be relevant to the work that was to be undertaken.

1.3.1 Existing catalytic methods of acylating sulfonamides

In the last decade the search for a more atom efficient method to acylate sulfonamides has begun to focus on metal catalysed reactions. The earliest example of heterogeneous catalysis for the *N*-acylation of sulfonamides was in reported in 2004.[51] The catalyst is an iron exchanged montmorillonite K10, FeO-K10. The catalyst is prepared by heating montmorillonite K10 clay with iron(III) chloride in acetonitrile at 120 ˚C for 5 hours prior to reacting with the substrates. Sulfonamides are then coupled to acid anhydrides in the presence of the catalyst. Good yields were recorded for various substrates, this was a good example of acid-catalysed acylation of sulfonamides. However, the process required to prepare the catalyst is extremely lengthy and consumes a vast amount of energy. The fact that this process is required before any acylations can take place is far from ideal.

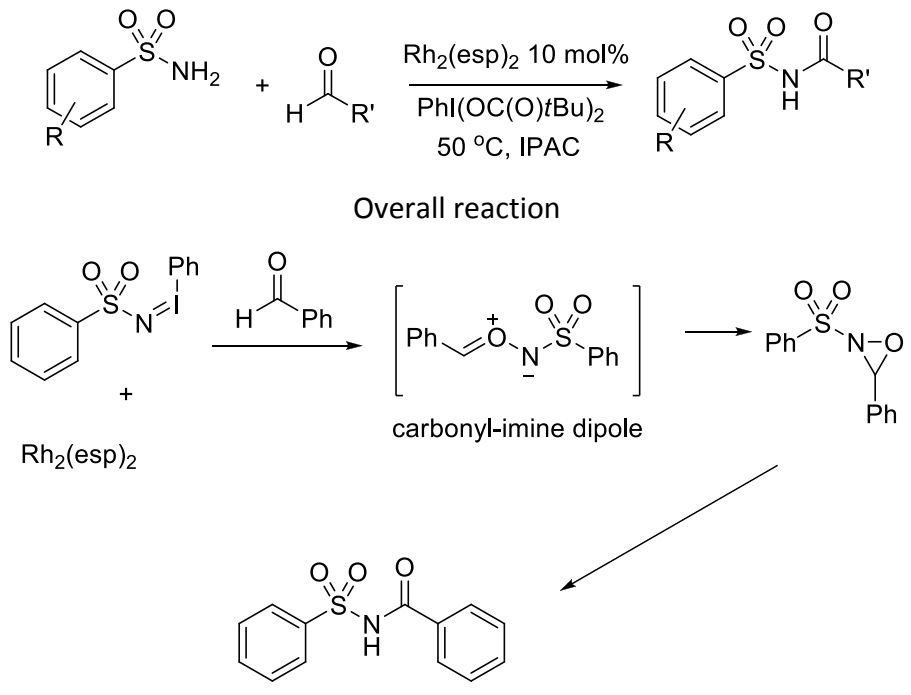
In 2005 Cho *et al.* looked at using copper iodide with alkynes, water and tosyl azides to generate *N*-acylsulfonamides as shown in Scheme 1.28.[52]



Scheme 1.28

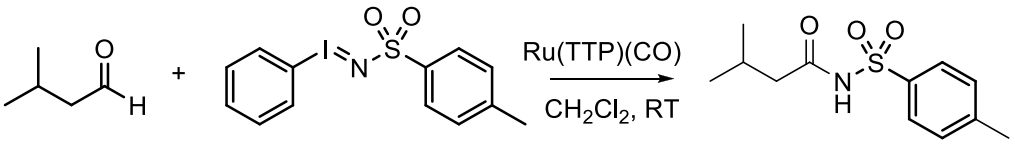
The mechanism for this reaction is not known but the group proposed that the copper catalyst forms the copper acetylide and that this under goes amination to form the *N*-sulfonyl ynamide. Subsequent addition of water to the allenamide tautomer gives the *N*-acylsulfonamide product, with the formation of N_2 as the driving force for the overall reaction. However, there are several fundamental problems with this method as an alternative synthetic route, the sulfonyl azides are not commercially available and will require prior synthesis.

In 2007 rhodium(II) was investigated in the oxidative coupling between sulfonamides and aldehydes.[53] The method requires an excess of aldehyde and one equivalent of an oxidant to be present, in this case the oxidant used is (diacetoxyiodo)benzene and the rhodium catalyst is $Rh_2(esp)_2$. The proposed pathway is shown in Scheme 1.29. There are some obvious disadvantages to this process, the main one being the cost, 1 g of the rhodium catalyst costs £260, and although this is used at 10 mol% it is not an industrially viable method of acylating sulfonamides. However, this cannot overshadow the large turnover numbers that this catalyst can achieve. Excellent yields are achieved and reported for some very challenging substrates, such as functional groups with strongly electron withdrawing groups and large bulky groups.



Scheme 1.29[53]

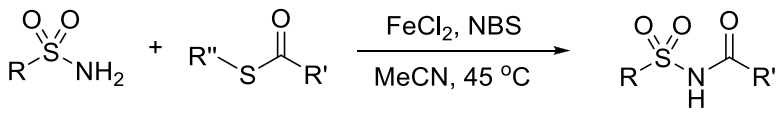
The development continued and in 2008 whilst searching for an efficient catalyst to synthesise amides Chan *et al.* developed a ruthenium(II) porphyrin catalyst that could successfully form *N*-acylsulfonamides in good yields.[54] This method involves the prior synthesis of, in their model reaction, *N*-tosyliminoiodinane. The reaction between the oxidising agent, $PhI(OAc)_2$, with a sulfonamide affords the corresponding iminoiodinane.[55] The *N*-tosyliminoiodinane is subsequently reacted with an aldehyde in the presence of the ruthenium catalyst as shown below in Scheme 1.30.



Scheme 1.30

Despite reported yields of 60-99% for a variety of aldehydes this method has some crucial drawbacks. Firstly the *N*-tosyliminoiodinane has to be synthesized and then two to four equivalents of it are required. Secondly the ruthenium catalyst also has to be prepared prior to use. However this is a good example of a metal catalysed reaction where the sulfonamide is activated by an oxidizing agent and results in good isolated yields.

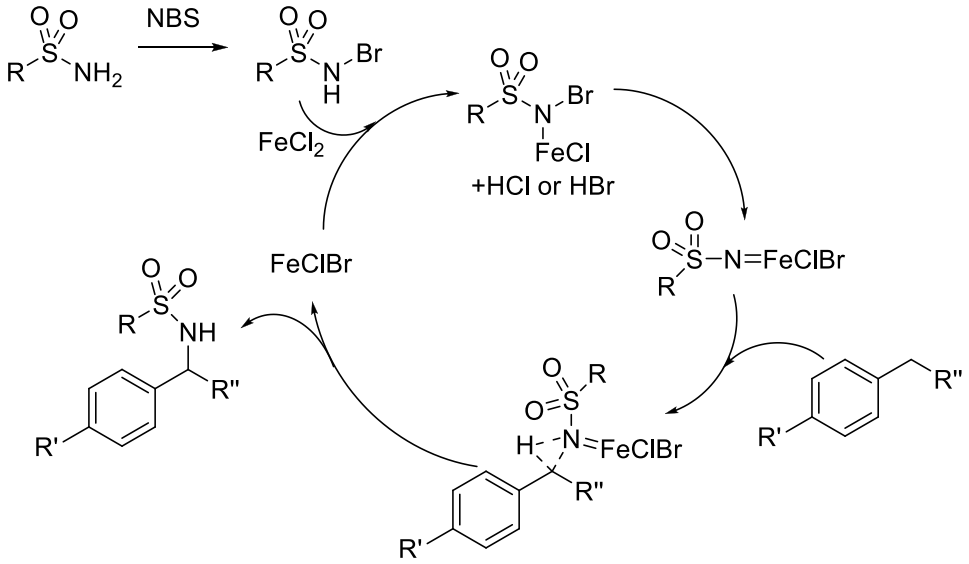
In 2009 Wang *et al.* investigated the potential of iron catalysed, NBS mediated coupling of sulfonamides and thioesters to form *N*-acylsulfonamides as well as synthesizing imides from thioesters and amides.[56]



Scheme 1.31

The amount of NBS required to achieve a good isolated yield varies from 0.4-1 equivalent, reaction times are typically 8-12 hours and yields were almost always >90%. This method showed that acylation of secondary sulfonamides could also be

achieved, although the isolated yield was 45%. No mechanism was put forward for how the coupling occurs, however in work carried out by Wang *et al.* a possible mechanism was proposed for the alkylation of sulfonamides using iron(II) chloride and NBS.[57] NBS, a good source of electrophilic bromine, was used to brominate the sulfonamide, the sulfonamide is then further activated by the iron(II) chloride and forms an iron-nitrene complex with the production of HCl or HBr. C-H bond activation occurs and the iron salt, the driving force of this reaction, is formed and recycles back to activate another halogenated sulfonamide. The full catalytic cycle is shown below in Scheme 1.32.



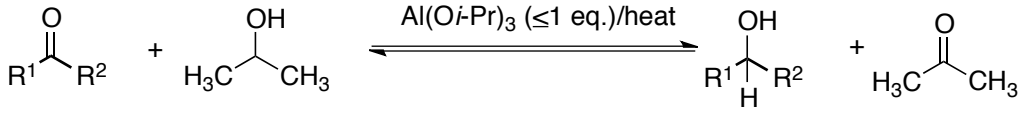
Scheme 1.32

It is therefore plausible that the bromination of the sulfonamide and subsequent formation of the iron-nitrene complex occurs in the acylation reaction and that the intermediate step involving the thioester results in the *N*-acyl product.

1.3.2 Transfer hydrogenation catalysts

The following section will show examples of transfer hydrogenation catalysts and, where appropriate, how they have been used to catalyse similar reactions to the *N*-acylation of sulfonamides. The definition of transfer hydrogenation is the addition of H_2 to a molecule from a source other than hydrogen gas.

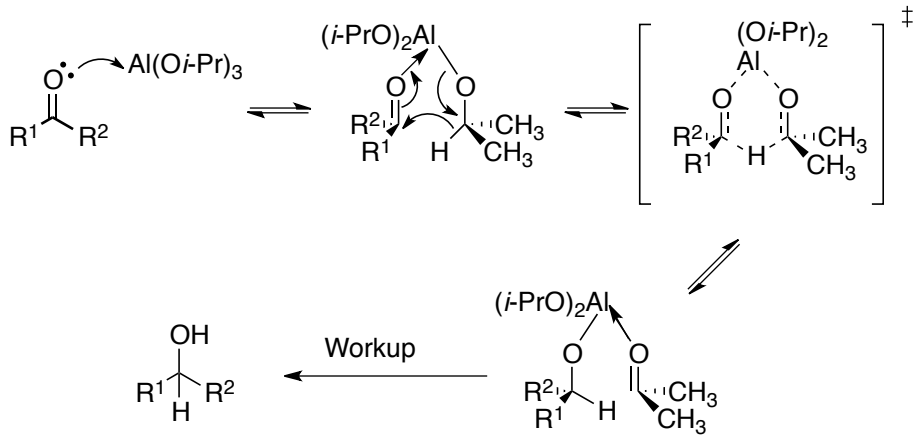
Meerwein-Ponndorf-Verley (MPV) reduction was an early example of metal catalysed transfer hydrogenation.[58] *Oppenauer* oxidation is the reverse of MPV,[59] hence the whole process is usually referred to as MPVO, where a substrate is oxidized or reduced and a sacrificial reagent is used as the corresponding reductant or oxidant as necessary, as shown in Scheme 1.33.



R^1 = alkyl, aryl, alkenyl; R^2 = H, alkyl, aryl, alkenyl

Scheme 1.33

The currently accepted mechanism involves a chair-like six-membered transition state is shown below in Scheme 1.34.[60]

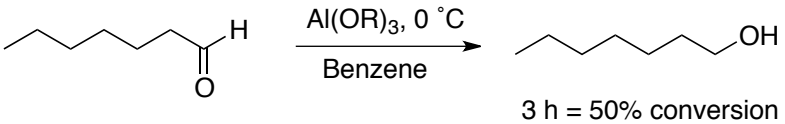


Scheme 1.34

The main problem with MPVO reactions is the reversibility of the process as shown in Scheme 1.34, this issue is in fact an equilibrium problem. Historically this has been overcome by using a large excess of alcohol to produce a low boiling point ketone that can easily be removed. This is why IPA is typically used as the alcohol, producing low boiling acetone that is easily removed from the reaction mixture. Kinetic data can provide greater insight into this problem,[61] by comparison of the oxidation potentials of ketones (product and starting ketones) one can determine an

approximate equilibrium position using equations for Gibbs free energy and the equilibrium constant. This can inform the choice of oxidant or reductant for a given substrate.

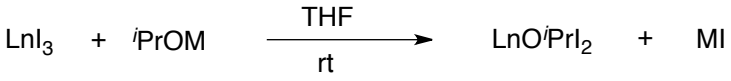
MPVO has been studied and modified over the past 90 years. One of the most significant modifications was to use TFA to enhance the rate of MPV and was presented in 1977 by *Rathke et al*.[62] The reaction is shown below in Scheme 1.34 shows that in the absence of TFA an aldehyde is slowly reduced to an alcohol, however, upon addition of a small amount of TFA the rate of reduction increases dramatically.



3 h = 50% conversion
5 mins (adding 0.5 eq. TFA) = 90% conversion

Scheme 1.35

Kagan et al. showed in 1984 the use of rare-earth metal salts for transfer hydrogenation reactions.[63] These catalysts were pre-prepared as shown in Scheme 1.36.

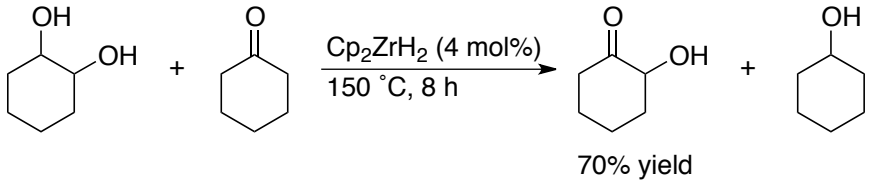


M = Na, Mg Ln = Sm, Ce, Yb

Scheme 1.36

The synthesized catalyst was then shown to successfully oxidize alcohols to ketones in yields around 90%. The reverse reductions could be achieved with comparable yields. A comprehensive review of lanthanide isopropoxides as catalysts for MPVO reactions was presented in 1987 by *Kiji et al.*[64] the complexes were tested for their catalytic activity. The results showed that Nd, Eu, Gd, Dy, Er, Tm and Yb isopropoxide were able to catalyse MPV reactions, with Gd(*i*PrO)$_3$ proving 10^3 times more active than the analogous aluminium catalyst.

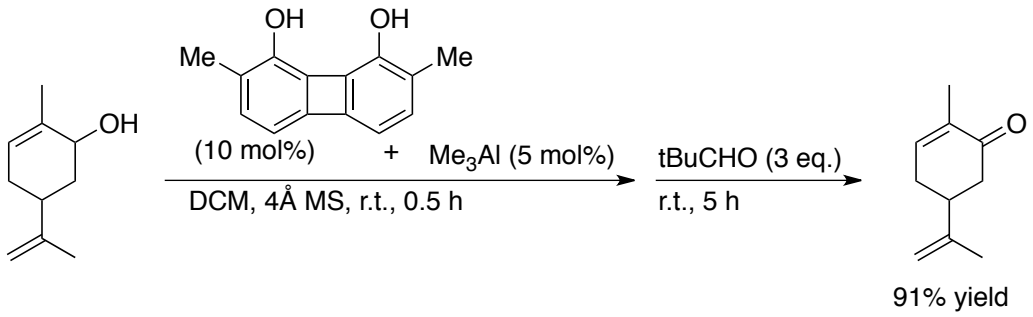
In 1986 *Ishii et al* presented two papers on the use of zirconocene dihydride to address one of the limitations of MPVO using traditional aluminium catalysts.[65] Aluminium catalysts typically showed no oxidation of diols.



Scheme 1.37

The example shown in Scheme 1.37 uses cyclohexanone as a hydrogen acceptor instead of acetone. Further selectivity was shown by *Ishii et al*. in 1987 when they showed the conversion of allylic alcohols into the corresponding α,β–unsaturated ketones and aldehydes using zirconocene dihydride.[66]

During the 1990s and early 2000s modifications to the alkoxide component of aluminium catalysts were made and reported by *Ooi et al*.[67]

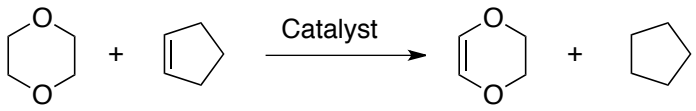


Scheme 1.38

One of the modifications is shown in Scheme 1.38, bidentate oxygen ligands were used to form aluminium pre-catalysts in this manner.[67b] They showed the ability to successfully oxidize a variety of alcohols.

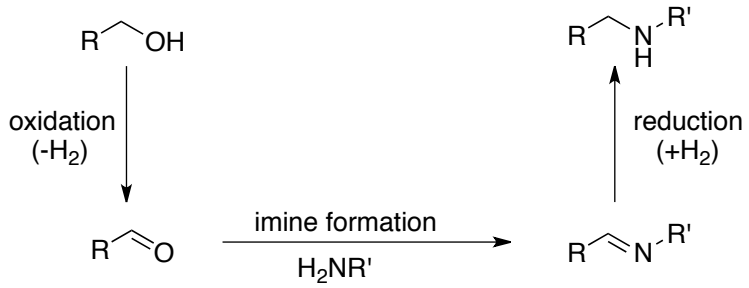
Since then work has been reported using a variety of metals to carry out modified MPVO reactions: Fe,[68] Pu,[69] B,[70] Mo,[71] Ni,[72] Sn[73] and Ti.[74]

Rhodium,[75] ruthenium[76] and iridium[77] have been investigated extensively in transfer hydrogenation reactions that do not proceed by the MPVO mechanism. Early work in the 1970s focused on the model reaction shown in Scheme 1.39 and investigating the activity of different metal catalysts.



Scheme 1.39

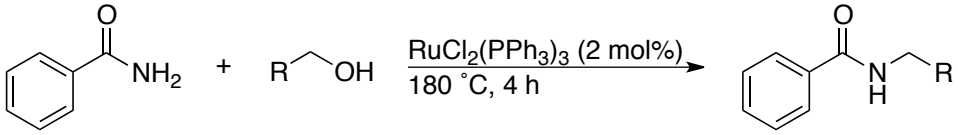
During the 1980s the focus switched to asymmetric transfer hydrogenation, which will be discussed in a later section of this introduction. Catalytic transfer hydrogenation, that was not MPVO, was not seriously investigated again until the mid-2000s when 'borrowing hydrogen' methodology was investigated more heavily.[78]



Scheme 1.40

Scheme 1.40 shows a general 'borrowing hydrogen' methodology, in this instance the reaction is the *N*-alkylation of an amine using benign alcohol as the alkylating agent, please see the review for the various catalysts using ruthenium and iridium.[78] The principle being that if one wished to alkylate an amine, traditionally one would require an alkyl halide reagent that are generally toxic and therefore using an alcohol starting material and producing water as the by-product was highly desirable.

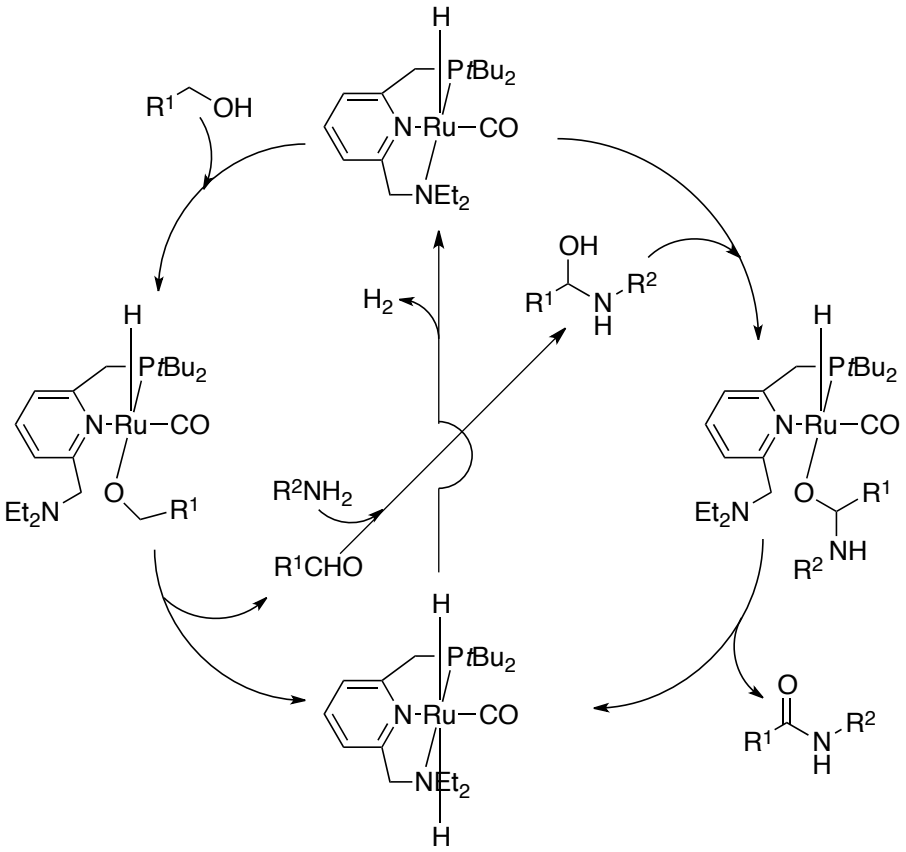
This naturally led to the consideration of other substrates that could be alkylated and whether alcohol could be used as the alkylating agent. Amides were considered as early as 1983 by *Watanabe et al.*[79] The reaction is shown in Scheme 1.41.



Scheme 1.41

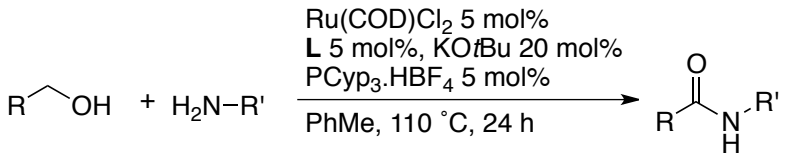
However, if the hydrogen wasn't 'borrowed' and was merely 'taken' by a hydrogen acceptor, then transfer hydrogenation would be performed. Unlike the previous investigations in the 1970s and 1980s though, the transformations investigated were on substrates of greater interest.

The first example of secondary amide formation from the coupling of amines and alcohols using catalytic transfer hydrogenation was presented in 2007 by *Milstein et al.*[80]



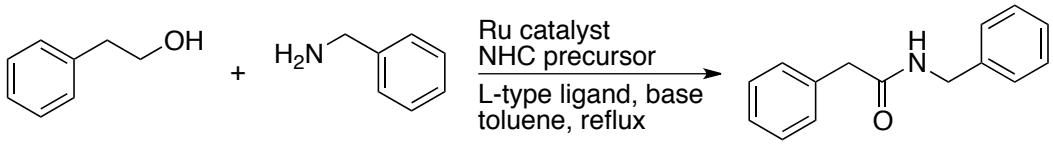
Scheme 1.42

Then in 2008 *Madsen et al.* investigated the same transformation, coupling amines and alcohols to form amides, using an alternative catalytic system, via the same proposed mechanism.[81]



Scheme 1.43

In 2009 *Ghosh et al.* looked at the coupling of alcohols and amines to form the secondary amide product as shown in Scheme 1.44[82]



Scheme 1.44

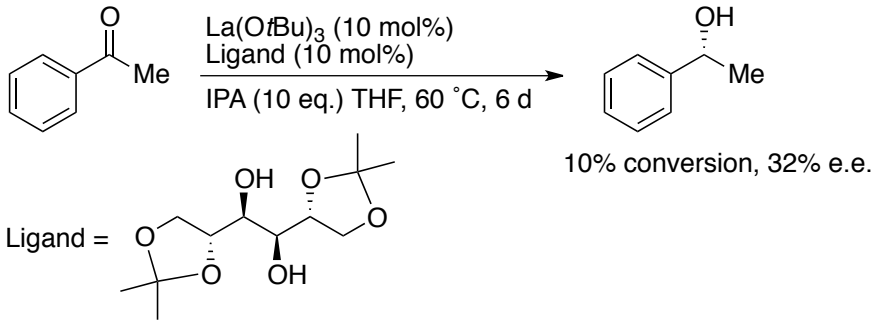
All these examples proceed through a hemiaminal intermediate that is thought to be stabilized by the ruthenium catalyst used.

1.4 Asymmetric transfer hydrogenation

With transfer hydrogenation in mind from the previous section, it is prudent to discuss the final area of homogeneous catalysis in this introduction, which is catalytic asymmetric transfer hydrogenation (ATH).

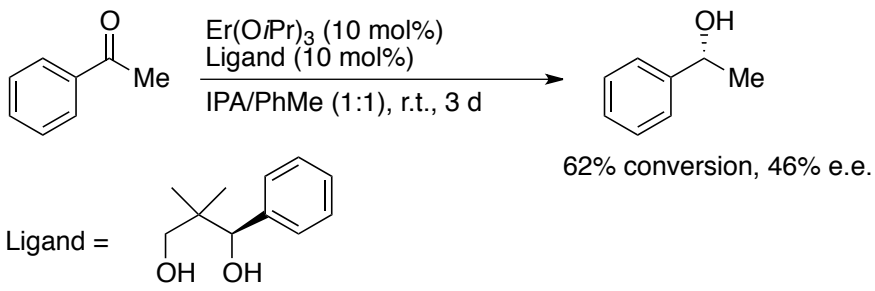
1.4.1 Asymmetric MPV reduction

Initially modifications to the existing MPV protocol were used to try to perform asymmetric reductions of ketones to synthesize enantiomerically enriched alcohols.[83]



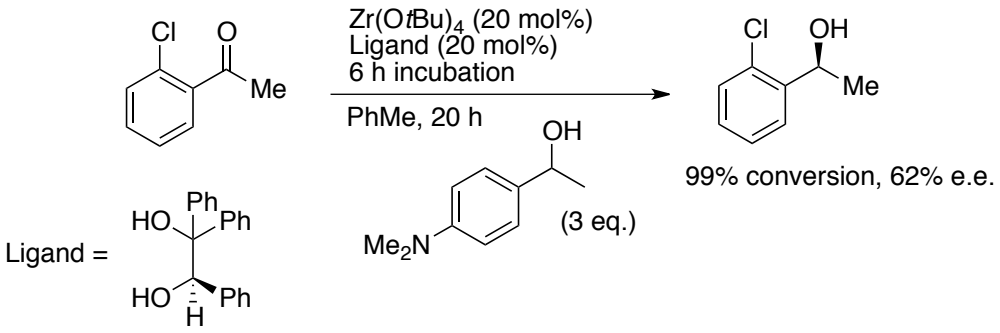
Scheme 1.45

The reaction, shown in Scheme 1.45, was carried out by *van Bekkum et al.* and gave a poor conversion and poor enantioselectivity using a lanthanum alkoxide complex with a 1,2-diol ligand system in an excess of IPA.[84] Improvements were made by *Kellogg et al.* who used erbium alkoxides with a prochiral 1,3-diol in IPA, shown in Scheme 1.46.[85] Both systems had lengthy reaction times though.



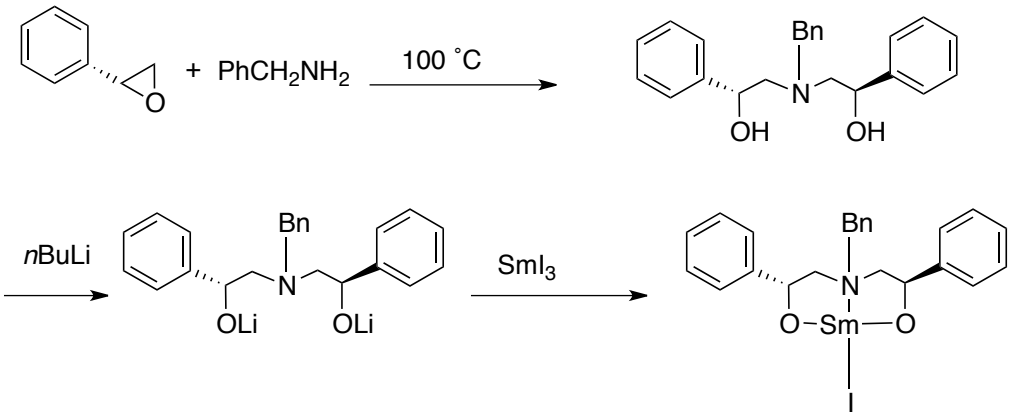
Scheme 1.46

Significant improvements were made by *Knaueur et al.* in 1995, they used an initial incubation period of six hours to preform the zirconium catalyst *in situ* before performing the reaction shown in Scheme 1.47 to obtain high conversion with moderate enantioselectivity.[86]



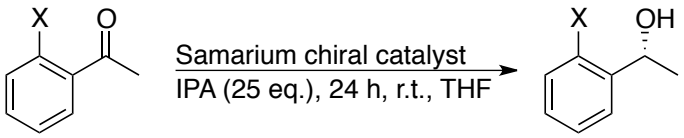
Scheme 1.47

Scheme 1.48 shows how *Evans et al.* synthesized their samarium chiral catalyst for MPV asymmetric reductions of aromatic ketones. The reaction conditions are shown in Scheme 1.49.[87]



Scheme 1.48

The enantioselectivity achieved represents the best that has so far been achieved using the modified MPV protocol for asymmetric reductions.

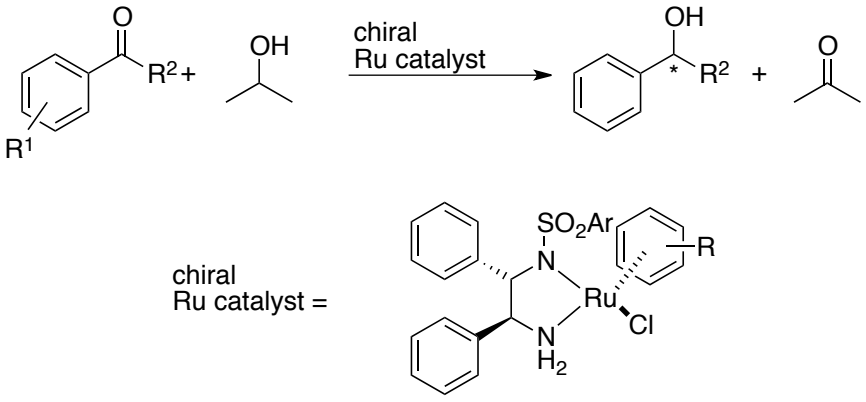


X = Cl, 96% conversion, 97% e.e.
X = H, 74% conversion, 96% e.e.
X = OMe, 95% conversion, 96% e.e.

Scheme 1.49

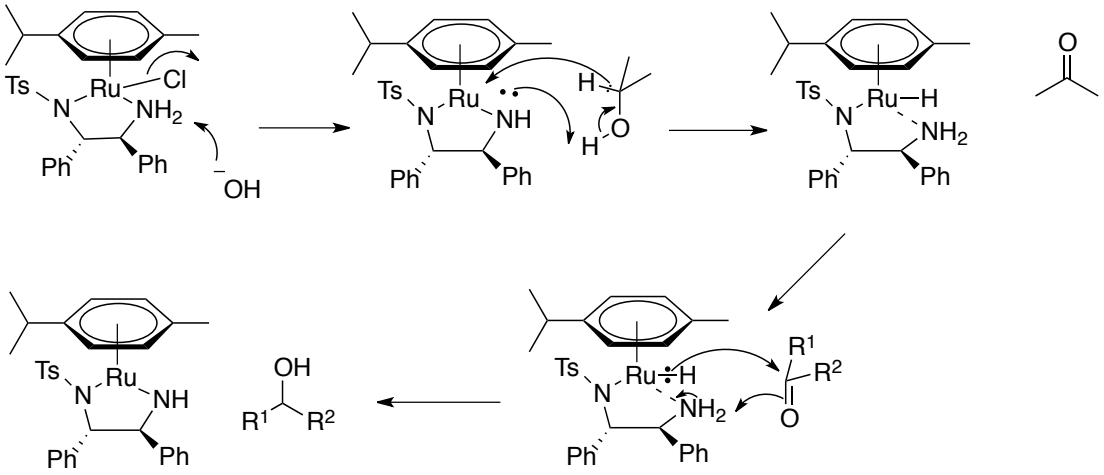
1.4.2 *Noyori's* ATH catalyst

The main focus of research into asymmetric transfer hydrogenation has been on the *Noyori* system. Scheme 1.50 shows the general reaction scheme taken from a review by Noyori in 1997.[88]



Scheme 1.50[88]

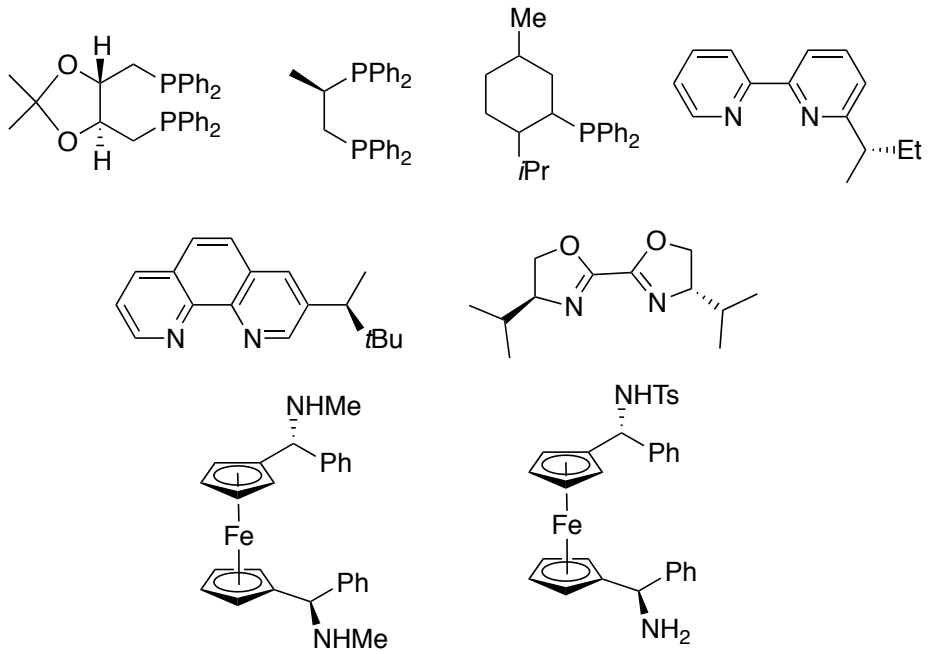
The most utilized derivative of the chiral catalyst shown in Scheme 1.50 is formed *in situ* from the reaction of dichlororuthenium(II)*p*-cymene dimer and TsDpen in the presence of a base, usually potassium hydroxide. Undergraduates study the mechanism for the asymmetric reduction and Scheme 1.51 shows the widely accepted mechanism.



Scheme 1.51

The chirality and steric bulk of the *in situ* catalyst dictates the direction of association of the substrate ketone, resulting in a chiral alcohol product.

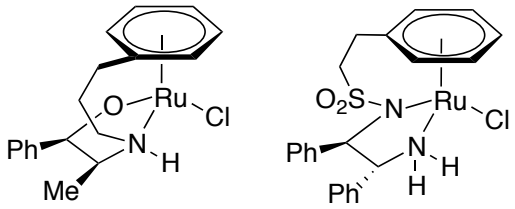
There are many variations to the system described here. Scheme 1.52 shows some of the ligands that have been investigated with rhodium,[89] iridium[90] and ruthenium[91] catalysts.



Scheme 1.52

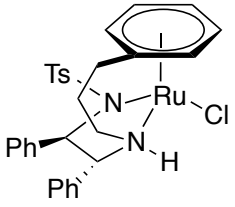
1.4.3 *Wills* modification to *Noyori* ATH system

In 2004 *Wills et al.* presented a new class of tethered ruthenium systems that were based on the successful *Noyori* catalyst system described above.[92] Wills had previously been investigating modifications to the *Noyori* system and provides a comprehensive summary of progress up to 1999 in his review.[93] The group's initial work focused on stabilizing the active catalyst species by locking the aryl system on the ruthenium centre to the ligand providing greater enantiomeric control over asymmetric reductions. The ligands that were investigated were monotosylated 1,2-diamines and β-amino alcohols.



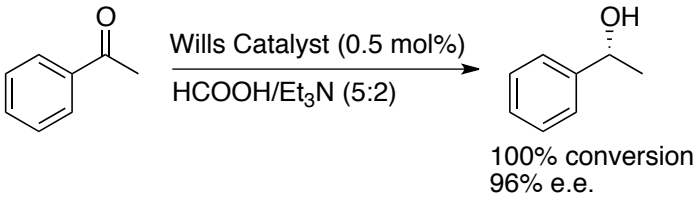
Scheme 1.53

The catalysts shown in Scheme 1.53 showed excellent activity achieving high conversions with high enantiomeric excess. Analogous rhodium(III) catalysts were also shown to have good activity.[94] In 2005 another form of the tethered catalyst had been synthesized and was shown to be significantly more active than the untethered catalyst and the two catalysts shown in Scheme 1.53.[95]



Scheme 1.54

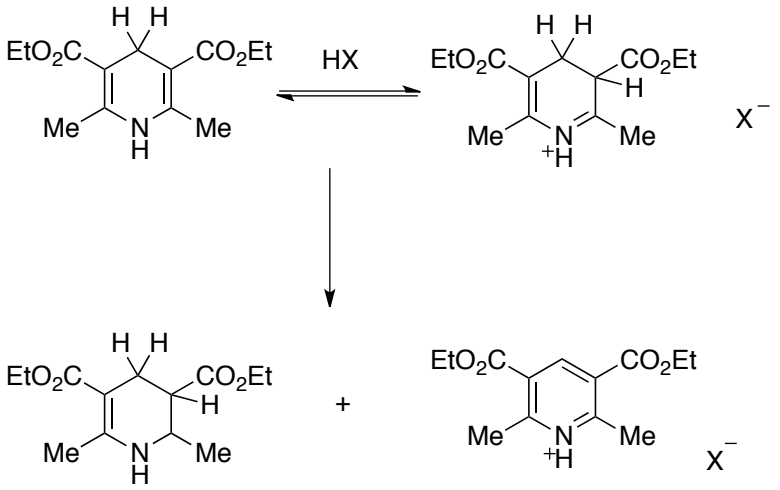
Scheme 1.54 shows the tethered catalyst that has since become Wills catalyst, the activity is shown in Scheme 1.55.



Scheme 1.55

In the final part of this introduction it is worth noting some of the different hydride or hydrogen sources that are used for asymmetric transfer hydrogenation as well as transfer hydrogenation. Shown in Scheme 1.55 is probably the most effective source of hydrogen other than the gas itself, which is an azeotrope of 5:2 formic acid to triethylamine, which is generally used as a solvent and avoids the need with IPA to have a very large excess to overcome the reversibility issue.[96]

Finally, Hantzsch esters are another source of hydrogen, the mechanism is shown below in Scheme 1.56.[97]



Scheme 1.56

1.5 Summary

Homogeneous catalysis is extremely important to both industrial and fine chemical synthesis. Research into new catalysts and catalytic systems is ongoing and receives significant attention throughout the literature. This introduction was to give the reader an overview of the various applications of homogeneous catalysis.

Existing methods to synthesize *N*-acylsulfonamides were summarized here and show that there is a need for a more atom efficient method of synthesis. Whether it is based on activating carboxylic acid derivatives or transfer hydrogenation reactions with alcohols.

Improvements to the activation of carboxylic acid derivatives would be desirable since this route usually involves stoichiometric amounts of waste and toxic coupling reagents. This would be of significant benefit to industrial synthesis as a significant amount of their synthetic pathways involve this type of activation.

Transfer hydrogenation reactions are also extremely desirable since hydrogen can be introduced to the product from a source other than hydrogen gas. Therefore the reaction does not need to be run under an atmosphere of hydrogen.

1.6 Project aims

The research presented in this thesis aims to address some of the problems with current *N*-acylsulfonamide synthesis outlined in previous sections. Specifically, the activation of carboxylic acid derivatives and also the acylation of sulfonamides using benign alcohol as the acylating agent, using low cost, commercially available reagents.

Results and Discussion I

Iodide as an Activating Agent

"Iodide as an Activating Agent for Acid Chlorides in Acylation Reactions"

Wakeham, R. J.; Taylor, J. E.; Bull, S. D.; Morris, J. A.; Williams, J. M. J., *Org. Lett.* **2013,** *15*, 702-705

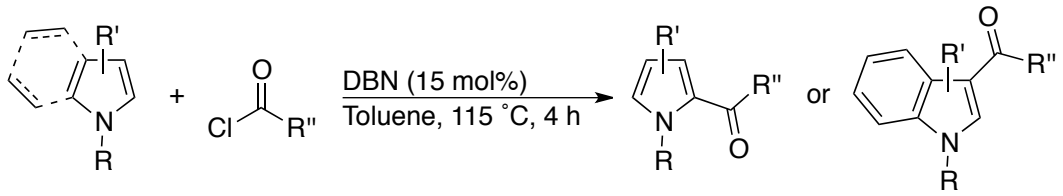
Iodide as an Activating Agent

Chapter 2: Results and Discussion I

2.1 Aims

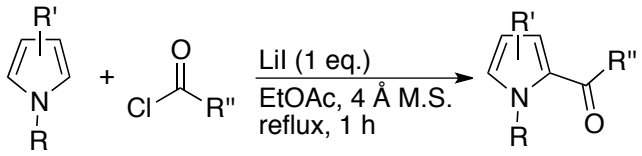
The aim of this work is to investigate whether acid chlorides can be activated, using an iodide source, towards nucleophilic attack from relatively poor nucleophiles. Sulfonamides are initially investigated but other nucleophiles are also considered.

Previous work in the group focused on DBN catalysed acylation using acid chlorides.[98] It was considered that acid chlorides form a complex with DBN and that this complex activates the acid chloride towards nucleophilic attack, as shown in Scheme 2.1.



Scheme 2.1

While screening additives that might enhance the yield and scope of the above reaction, lithium iodide was seen to enhance the reactivity of the DBN reaction, furthermore in the absence of DBN, with one equivalent of iodide the reaction proceeds to completion.



Scheme 2.2

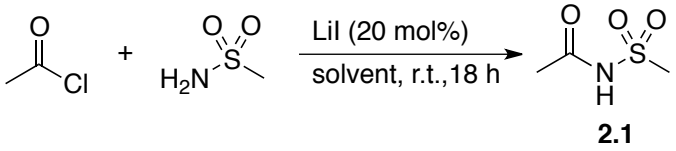
The aim of this work is therefore to investigate the potential scope for iodide activation and to probe the reaction further to determine any mechanistic information that can be obtained.

2.2 Initial work

2.2.1 Sulfonamides

Sulfonamides are relatively poor nucleophiles owing to the electron-withdrawing nature of the adjacent -SO_2 group to the -NH_2 thereby acting to stabilize the lone pair on the nitrogen.

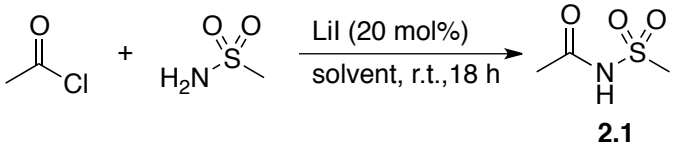
To begin with it was investigated whether the following reaction would proceed catalytically at room temperature.



2.1

Scheme 2.3

The percentage conversion of reactants into *N*-acylsulfonamide **2.1** is determined by analysis of relative integration of the peaks corresponding to the methyl CH_3 of methanesulfonamide, at δ 3.15 ppm and the methyl CH_3 of *N*-acetylmethansulfonamide at δ 3.25 ppm in the ^{1}H NMR. The initial amount of lithium iodide, 20 mol%, was chosen arbitrarily and a series of dry solvents was screened, summarized in Table 2.1.



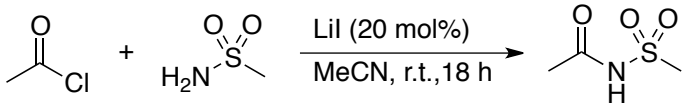
2.1

Entry	Solvent[a]	*N*-Acylsulfonamide **2.1** conversion[b] (%)
1	PhMe (anhydrous)	46
2	MeCN (anhydrous)	94
3	DCM (anhydrous)	57
4	Et_2O (anhydrous)	93
5	EtOAc (4 Å MS)	89

Table 2.1. [a] Reactions were performed on a 2 mmol scale in 2 mL solvent. [b]Conversions determined by analysis of the ^{1}H NMR spectra.

Although similar results are observed for Et_2O (Table 2.1, entry 4) and MeCN **T**able 2.1, entry 2), MeCN is chosen as the solvent because of its higher boiling point 82 ˚C.

The amount of lithium iodide was varied to determine whether a lower amount would still form the *N*-acylated product. It was pleasing that 0.1 mol% lithium iodide (Table 2.2, entry 2) gave 86% conversion into compound **2.1**. However, it was also noted that in the absence of lithium iodide, 73% conversion into compound **2.1** was observed (Table 2.2, entry 1).



2.1

Entry	LiI[a] (mol%)	*N*-Acylsulfonamide **2.1** conversion[b] (%)
1	0	73
2	0.1	86
3	1	84
4	2	88
5	5	83
6	10	86
7	20	94

Table 2.2. [a] Reactions were performed on a 5 mmol scale in 5 mL solvent. [b]Conversions determined by analysis of the ^{1}H NMR spectra.

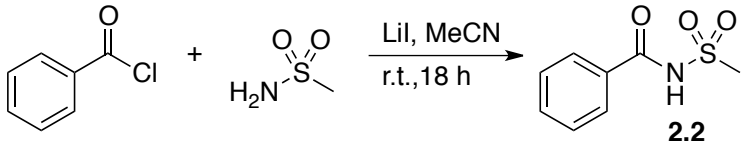
Whilst it was apparent that the presence of lithium iodide does alter the conversion, the background rate is very high. It is known that acetyl chloride is extremely reactive to nucleophilic attack, this is because the δ^+ on the carbonyl carbon has a readily accessible π^* (C=O) orbital to an incoming nucleophile and the inductive effect of a single methyl group would not affect this significantly, either electronically or sterically. Hence a more challenging electrophile was required to provide a greater contrast between the presence and absence of an activating agent. Benzoyl chloride was chosen since it is less reactive than acetyl chloride. This can be

understood by considering the resonance structures of benzoyl chloride, Scheme 2.4.

Scheme 2.4

The delocalization around the phenyl ring results in stabilization of the positive charge, therefore unlike in acetyl chloride, the positive charge is not concentrated on the carbonyl carbon and benzoyl chloride is therefore less electrophilic than acetyl chloride.

However, acylation of methanesulfonamide using benzoyl chloride to form compound **2.2** was unsuccessful at room temperature over 18 hours (Table 2.3, entry 1).

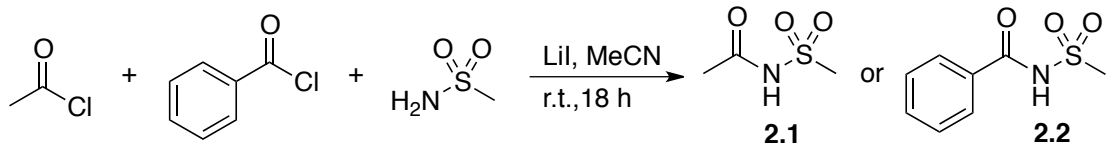


2.2

Entry	LiI[a] (mol%)	*N*-Acylsulfonamide **2.2** conversion[b] (%)
1	20	<5
2	100	36
3	100	38[c]

Table 2.3. [a] Reactions were performed on a 1 mmol scale in 1 mL MeCN. [b] Conversions determined by analysis of the ^{1}H NMR spectra. [c]Reaction carried out at 40 ˚C on a 2 mmol scale in 2 mL MeCN.

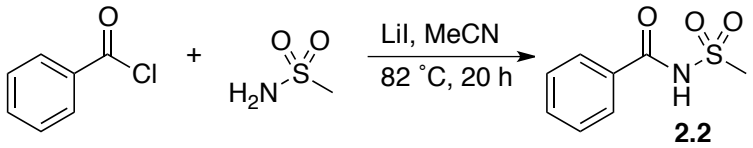
Increasing the amount of lithium iodide to one equivalent was an improvement but insufficient because the conversion into compound **2.2** is only 36% (Table 2.3, entry 2). A competition experiment was carried out between acetyl and benzoyl chloride, Scheme 2.5.



Scheme 2.5

This showed that *N*-acylsulfonamide **2.1** is produced exclusively, with a conversion of 79%. This confirms the lower electrophilicity of benzoyl chloride and the preference of a sulfonamide nucleophile for acetyl chloride.

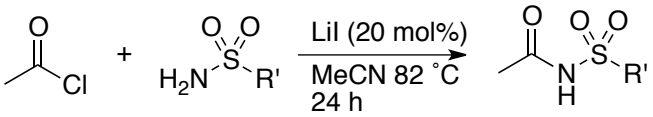
Returning to the reaction of benzoyl chloride with methanesulfonamide, increasing the temperature to 40 ˚C only increased the conversion to 38% (Table 2.3, entry 3), however upon heating to reflux and extending the reaction time, higher conversions could be obtained (Table 2.4). When the amount of lithium iodide is again reduced to catalytic levels conversion into *N*-acylsulfonamide **2.2** improves over the background rate with excellent turnover observed at 20 mol% catalyst loading (Table 2.4, entry 6) and quantitative conversion is achievable with an excess of lithium iodide (Table 2.4, entry 8).



Entry	LiI[a] (mol%)	*N*-Acylsulfonamide **2** conversion[b] (%)
1	0	16
2	1	64
3	2	79
4	5	84
5	10	89
6	20	91
7	100	95
8	150	100

Table 2.4. [a] Reactions were performed on a 2 mmol scale in 2 mL solvent. [b]Conversions determined by analysis of the ^{1}H NMR spectra.

Extending the reaction time to 24 hours and increasing the amount of acid chloride to 1.2 equivalents of the nucleophile provided the optimized conditions. The substrate scope was investigated and the sulfonamide nucleophile was varied with acetyl chloride as the electrophile.



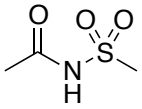
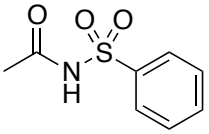
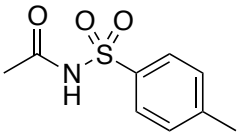
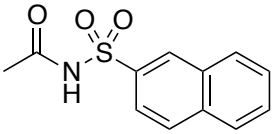
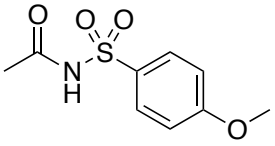
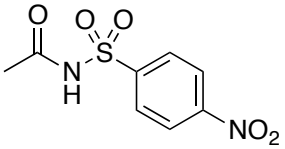
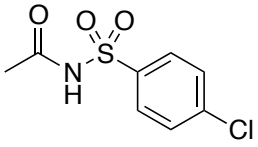
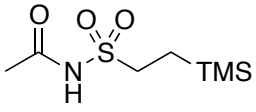
Entry	Compound[a]	*N*-Acylsulfonamide	Yield[b] (%)
1	**2.1**		19(94)
2	**2.3**		84
3	**2.4**		94
4	**2.5**		90
5	**2.6**		90
6	**2.7**		87
7	**2.8**		83
8	**2.9**		90

Table 2.5. [a]Reactions were performed on a 5 mmol scale, using 6 mmol of acid chloride in 2 mL solvent. [b]Isolated yields, products purified by column chromatography, conversions, in parentheses, determined by analysis of the ^{1}H NMR spectra.

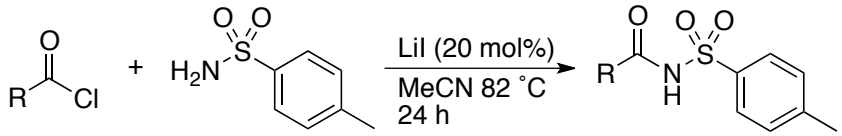
Table 2.5 shows that the nature of the sulfonamide nucleophile has very little impact on the yield of *N*-acylsulfonamide, reinforcing the reactivity of the electrophile, acetyl chloride.

Aliphatic sulfonamides would be expected to give higher yields based on electronic arguments. The inductive effect of an alkyl group donates electron density to the π^* (S=O) orbital on the sulfonyl sulfur reducing the stabilization of the nitrogen lone pair, hence they are better nucleophiles. However, methanesulfonamide gave a lower than expected yield for the reaction (Table 2.5, entry 1). The experiment was repeated several times and always yields the same 19% isolated yield despite the observed conversion of 94%. The reason for this could be attributed to the method of purification. Methyl esters are susceptible to acid catalysed hydrolysis on acidic silica, the analogous *N*-acetylmethanesulfonamide is also susceptible.

Aromatic sulfonamides behave as expected with the more electron rich sulfonamides, such as 4-methoxybenzene sulfonamide (Table 2.5, entry 6), giving the highest isolated yield, conversely the most electron withdrawing aromatic sustituents, 4-nitro and 4-chloro benzene sulfonamide (Table 2.5, entries 7 & 8) respectively) are produced in slightly lower yields.

However, it is important to note that the reactivity of acetyl chloride is the predominant factor for the results in Table 2.5.

In Table 2.6 the acid chloride is varied and the nucleophile, *p*-toluenesulfonamide, is fixed. The results raise a problem: aliphatic acid chlorides (considerably more reactive) showed excellent coupling to *p*-toluenesulfonamide; however, aromatic acid chlorides (relatively less reactive), such as benzoyl chloride, showed poor reactivity with a conversion into the *N*-acylsulfonamide **2.10** of 13% (Table 2.6, entry 1). This is attributed to the difference between the nucleophilicity of methanesulfonamide and *p*-toluenesulfonamide (*N*-acylsulfonamide **2.2** & **2.10**, conversions 91 & 13% respectively (Table 2.5, entry 1 & Table 2.6, entry 1).



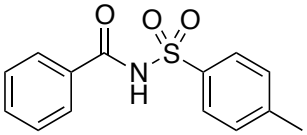
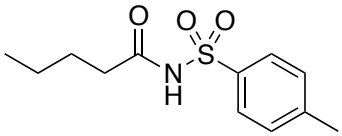
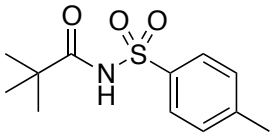
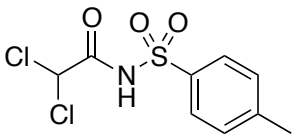
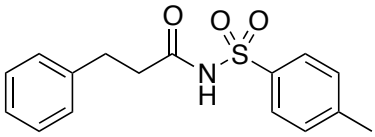
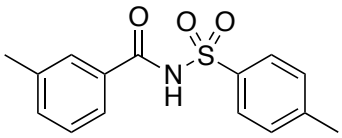
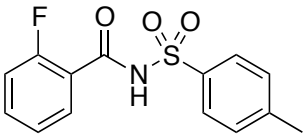
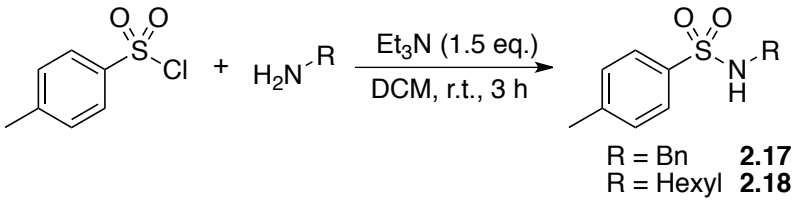
Entry	Compound[a]	*N*-Acylsulfonamide	Conversion[b] (%)
1	**2.10**		13
2	**2.11**		98
3	**2.12**		86
4	**2.13**		61
5	**2.14**		97
6	**2.15**		22
7	**2.16**		<5

Table 2.6. [a]Reactions were performed on a 5 mmol scale, using 6 mmol of acid chloride in 2 mL solvent. [b]Conversions determined by analysis of the ^{1}H NMR spectra.

Aliphatic acid chlorides give high conversions, consistent with their reactivity. The relatively lower conversion for trimethylacetyl chloride (Table 2.6, entry 3) can be attributed to the steric hindrance around the carbonyl carbon hindering attack from the nucleophile and inductive effects from three methyl groups reducing δ^+ on the carbonyl carbon. Further optimization would be required to obtain high conversions for the less reactive acid chlorides.

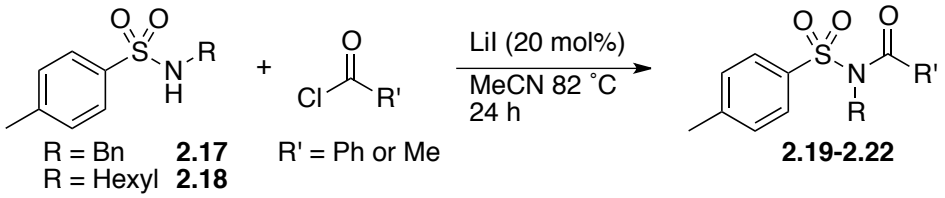
2.2.2 Secondary Sulfonamides

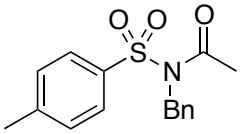
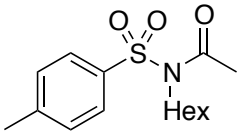
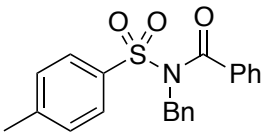
Secondary sulfonamide starting materials were synthesized so that the acylation of a secondary sulfonamide could be investigated. Below in Scheme 2.6 is the general reaction for the synthesis of secondary sulfonamides.



Scheme 2.6

Using the optimized reaction conditions, acetyl and benzoyl chloride were reacted with secondary sulfonamides **2.17** & **2.18**. The experiments were also carried out in the absence of lithium iodide to give a background rate for this reaction. The results are summarized in Table 2.7.



Entry	Compound[a]	*N*-Acylsulfonamide	Conversion[b] (%)
1	**2.19**		78(25)
2	**2.20**		83(39)
3	**2.21**		<1(0)

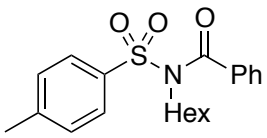
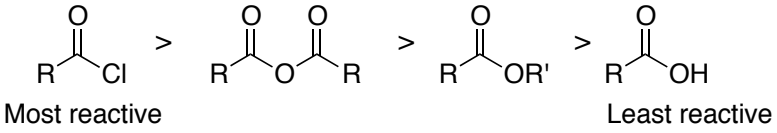
4	**2.22**		0(0)

Table 2.7. [a]Reactions were performed on a 5 mmol scale, using 5 mmol of acid chloride in 2 mL solvent. [b]Conversions determined by analysis of the ^{1}H NMR spectra, figures in parentheses are reactions performed in the absence of lithium iodide.

No reaction between benzoyl chloride and either of the secondary sulfonamides was observed (Table 2.7, entries 3 & 4). Given the poor reaction between the primary sulfonamide and benzoyl chloride this was expected. Since secondary sulfonamides are more hindered nucleophiles than primary ones they are less nucleophilic.

The reaction between acetyl chloride and compounds **2.17** & **2.18** (Table 2.7, entries 1 & 2) succeeded and it was pleasing that there is a marked improvement over the background rate.

2.2.3 Reactivity of the acid derivative series

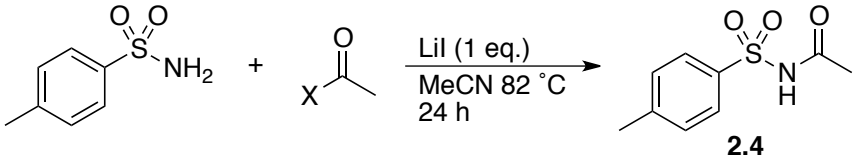


Scheme 2.7

Lithium iodide was tested to determine if others in the acid series are activated in a similar manner to the most reactive, acid chloride. The trend is shown in Scheme 2.7.

Acetyl chloride and acetic anhydride were the only members of the acid derivative series to show activity under these conditions. Ester and caboxylic acid groups were not activated by lithium iodide (Table 2.8, entries 2 & 3) and therefore no further investigations were carried out into them. Acetic anhydride is sufficiently reactive that in the presence and absence of lithium iodide 81% conversion was observed for both (Table 2.8, entry 1). However further investigations into anhydride activation

using iodide sources have been carried out within the group and will not be discussed here.



2.4

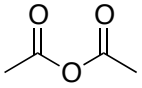
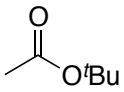
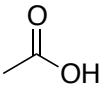
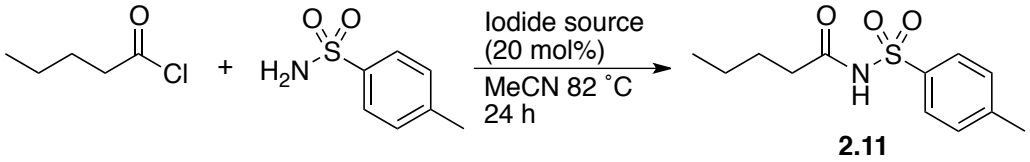
Entry	Acid derivative[a]	*N*-Acylsulfonamide **2.4** conversion[b] (%)
1		81(81)
2		0(0)
3		0(0)

Table 2.8. [a]Reactions were performed on a 2 mmol scale, using 2.4 mmol of acid chloride in 2 mL solvent. [b]Conversions determined by analysis of the ^{1}H NMR spectra, figures in parentheses are reactions performed in the absence of lithium iodide.

2.3 Potassium iodide

2.3.1 Sulfonamides

At this stage the low conversion observed with benzoyl chloride and *p*-toluenesulfonamide (Table 2.6, entry 1) needed to be revisited. A screen of iodide sources was undertaken to determine if lithium iodide is the best source. Initially the reaction between valeroyl chloride and *p*-toluenesulfonamide was investigated and the results are shown in Table 2.9.

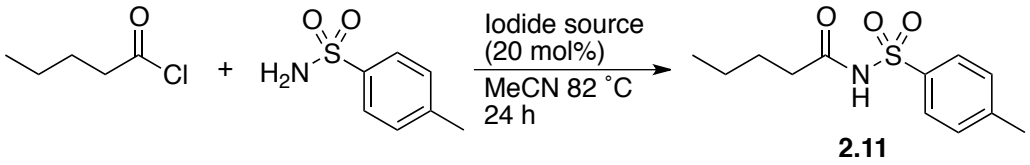


2.11

Entry	Iodide source[a]	*N*-Acylsulfonamide **2.11** conversion[b] (%)
1	No Iodide	91
2	LiI	86
3	NaI	97
4	KI	100
5	NH_4I	97
6	CuI_2	87
7	FeI_2	52
8	ZnI_2	94
9	I_2	66

Table 2.9. [a] Reactions were performed on a 1 mmol scale, using 1.2 mmol of acid chloride in 1 mL solvent. [b]Conversions determined by analysis of the ^{1}H NMR spectra.

Other salts were considered to see if iodide is just a counter-ion or whether it is important in the activation of the acid chloride.

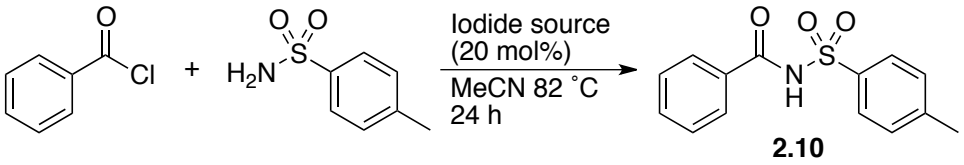


2.11

Entry	Salt[a]	*N*-Acylsulfonamide **2.11** conversion[b] (%)
1	No salt	91
2	KBr	100
3	KCl	97
4	$AlCl_3$	96

Table 2.10. [a] Reactions were performed on a 1 mmol scale, using 1.2 mmol of acid chloride in 1 mL solvent. [b]Conversions determined by analysis of the ^{1}H NMR spectra.

Lithium iodide shows decreased activity (Table 2.9, entry 2) compared to the absence of an iodide source (Table 2.9, entry 1). However, quantitative conversion into the *N*-acylsulfonamide is achieved using potassium iodide (Table 2.9, entry 4). Tables 2.9 & 2.10 highlight that the contrast between the background rate and the catalysed rate is too close to properly assess the relative activities and therefore screening is carried out with the less reactive benzoyl chloride.



2.10

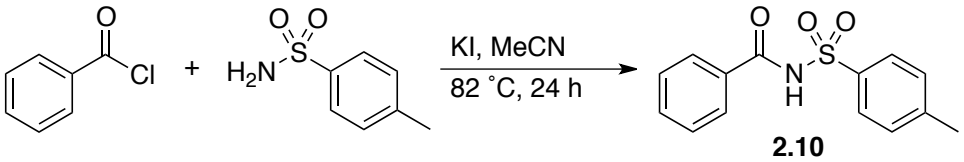
Entry	Iodide source[a]	*N*-Acylsulfonamide **2.10** conversion[b] (%)
1	No Iodide	7
2	LiI	13
3	NaI	78
4	KI	69
5	RbI	46
6	CsI	18
7	NH_4I	61
8	*n*-Bu_4NI	10

Table 2.11. [a] Reactions were performed on a 1 mmol scale, using 1.2 mmol of acid chloride in 1 mL solvent. [b]Conversions determined by analysis of the ^{1}H NMR spectra using 2,5-dimethylfuran as an internal standard.

The results show that there is a large contrast between the absence of an iodide source (Table 2.11, entry 1) and the presence of either sodium iodide (Table 2.11, entry 3) or potassium iodide (Table 2.11, entry 4). The conversion achieved with lithium iodide is consistent with those remarked on earlier (Table 2.11, entry 2). Although lithium iodide showed some promise as an activating agent for acid chlorides in some situations, sodium and potassium iodide performed much better under the conditions shown in Table 2.11.

Potassium iodide was optimized, given the cheaper cost relative to sodium iodide at the time of conducting these experiments. However, sodium iodide appears to work just as well and sometimes better and therefore they could be interchanged if required.

The amount of potassium iodide was investigated, 60 mol% provided quantitative conversion (Table 2.12, entry 10). The full results are detailed in Table 2.12.



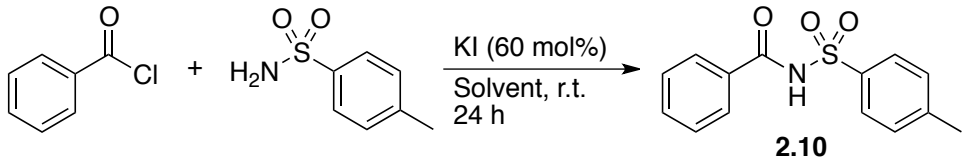
2.10

Entry	KI (mol%)[a]	*N*-Acylsulfonamide **2.10** conversion[b] (%)
1	0	12
2	1	20
3	2	25
4	5	36
5	10	30
6	20	67
7	30	63
8	40	62
9	50	80
10	60	100
11	70	70
12	80	87
13	90	84
14	100	57
15	150	68
16	200	65

Table 2.12. [a] Reactions were performed on a 1 mmol scale, using 1.2 mmol of acid chloride in 1 mL solvent. [b]Conversions determined by analysis of the ^{1}H NMR spectra using 2,5-dimethylfuran as an internal standard.

Increasing the amount of potassium iodide did not improve the conversion and actually inhibited it. There is no obvious explanation for this at this stage.

A solvent screen was carried out to establish the best solvent for potassium iodide. Interestingly the results are very different to Table 2.1, only MeCN and EtOAc (Table 2.13, entries 2 & 7) showed acylation product.

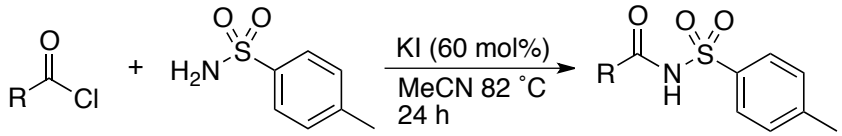


2.10

Entry	Solvent[a]	*N*-Acylsulfonamide **2.10** conversion[b] (%)
1	PhMe	0
2	MeCN	46
3	Hexane	0
4	THF	0
5	Et_2O	0
6	DCM	0
7	EtOAc	14
8	DMSO	0
9	DMF	0

Table 2.13. [a] Reactions were performed on a 1 mmol scale, using 1.2 mmol of acid chloride in 1 mL solvent. [b]Conversions determined by analysis of the ^{1}H NMR spectra using 2,5-dimethylfuran as an internal standard.

The substrate scope was investigated using the optimized conditions for potassium iodide. Table 2.14 shows the results for the addition of *p*-toluenesulfonamide to various acid chlorides. Table 2.15 shows the results for the addition of various sulfonamides to benzoyl chloride.



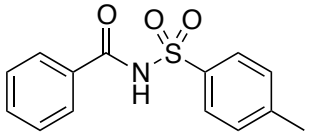
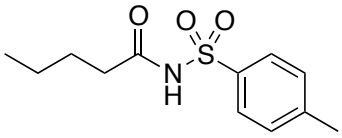
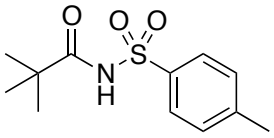
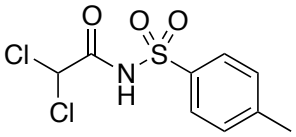
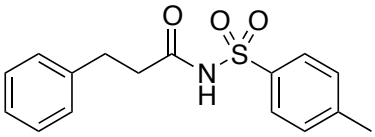
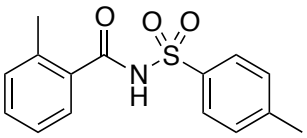
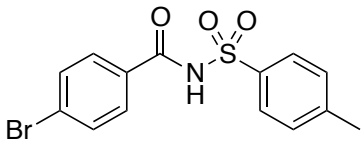
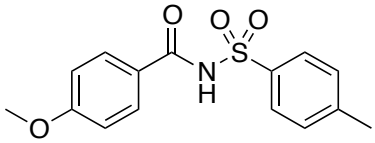
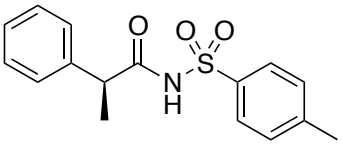
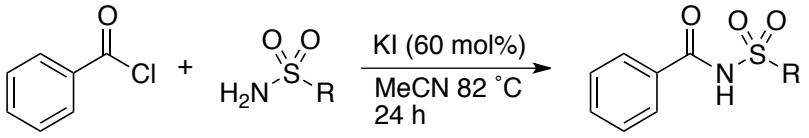
Entry	Compound[a]	*N*-Acylsulfonamide	Yield[b] (%)
1	**2.23**		89
2	**2.24**		88
3	**2.25**		80
4	**2.26**		41
5	**2.27**		91
6	**2.28**		92
7	**2.29**		67
8	**2.30**		97
9	**2.31**		54[c](80% e.e.)

Table 2.14. [a]Reactions were performed on a 3 mmol scale, using 3.6 mmol of acid chloride in 3 mL solvent. [b]Isolated yields, products purified by column chromatography. [c]Isolated by prep. HPLC.



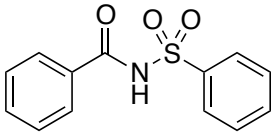
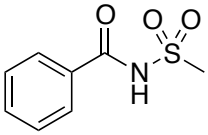
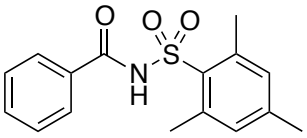
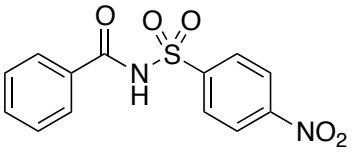
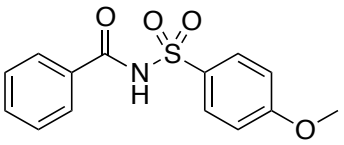
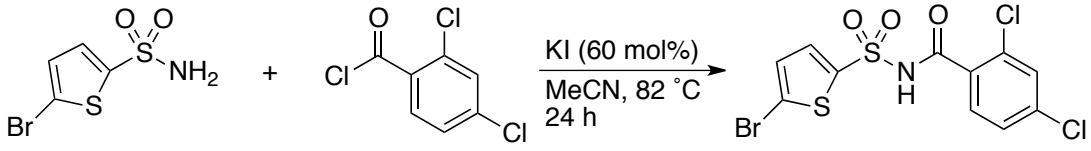
Entry	Compound[a]	*N*-Acylsulfonamide	Yield[b] (%)
1	**2.32**		96
2	**2.33**		83[c]
3	**2.34**		73
4	**2.35**		78
5	**2.36**		83

Table 2.15. [a]Reactions were performed on a 3 mmol scale, using 3.6 mmol of acid chloride in 3 mL solvent. [b]Isolated yields, products purified by column chromatography. [c]Isolated after recrystallisation ($EtOH/H_2O$).

Tables 2.14 & 2.15 show that both aliphatic and aromatic acid chlorides were found to be suitable substrates, as were aromatic and aliphatic sulfonamides. Electron withdrawing and electron donating aromatic acid chlorides and sulfonamides were also tolerated. Excellent yields were obtained with steric bulk on the sulfonamide and acid chloride. There was partial racemization in the formation of the chiral product (Table 2.14, entry 9). However, as the product was not racemic this suggests that the reaction did not proceed wholly via a ketene intermediate. Although large amounts of iodide were needed in order to achieve a significant beneficial rate enhancement, the optimized conditions represent an excellent method of forming *N*-acylsulfonamides.

The method could now be incorporated into the synthesis of a molecule that has been investigated as an Anti-proliferative agent,[99] Scheme 2.8.

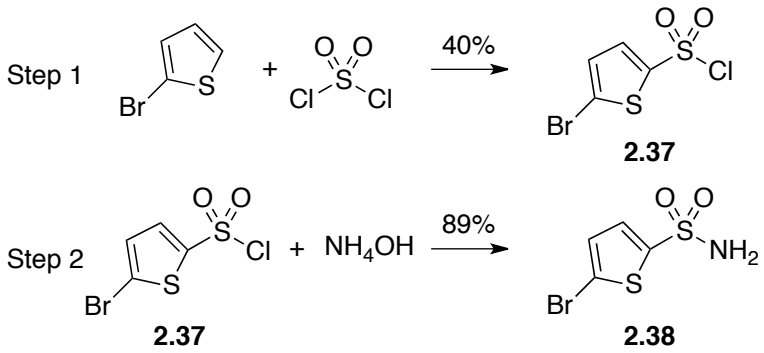


2.38 **2.39**

Scheme 2.8

The existing method relies on the use of catalytic DMAP to couple the acid chloride to the corresponding sulfonamide. It was therefore of interest to investigate whether one could couple the sulfonamide and acid chloride using the cheaper and significantly less toxic potassium iodide.

Initially the sulfonamide was synthesized starting from 2-bromothiophene, the synthesis is detailed in Scheme 2.9**.**



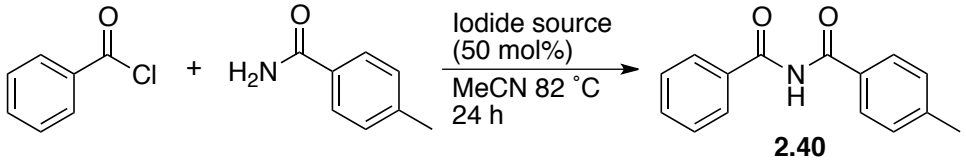
2.37 **2.37** **2.38**

Scheme 2.9

The final step of the synthesis is the coupling of the acid chloride and the sulfonamide as shown in Scheme 2.8. The isolated yield for this step is a disappointing 19%, which equates to an overall yield of 7%.

2.3.2 Amides

The acylation of amides using acid chlorides is another reaction that generally requires an activating agent. Since the previous effort with lithium iodide only worked for acetyl chloride, an iodide source screen was carried out on the reaction between *p*-toluamide and benzoyl chloride. Amides are less nucleophilic than sulfonamides owing to the better overlap of orbitals between the lone pair on the nitrogen and π^* (C=O) carbonyl carbon orbital. This orbital overlap stabilizes the lone pair on the nitrogen reducing the nucleophilicity.

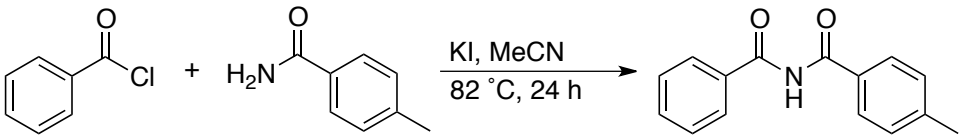


2.40

Entry	Iodide source[a]	Imide **2.40** conversion[b] (%)
1	No Iodide	4
2	LiI	10
3	NaI	18
4	KI	27
5	RbI	14
6	CsI	7
7	NH_4I	19
8	*n*-Bu_4NI	10

Table 2.16. [a] Reactions were performed on a 1 mmol scale, using 1.2 mmol of acid chloride in 1 mL solvent. [b]Conversions determined by analysis of the ^{1}H NMR spectra using 2,5-dimethylfuran as an internal standard.

Potassium iodide (Table 2.16, entry 4) showed the best activity, however, at 50 mol% the conversion into imide **2.40** is only 27%. The concentration of potassium iodide was varied; the results are shown in Table 2.17.



2.40

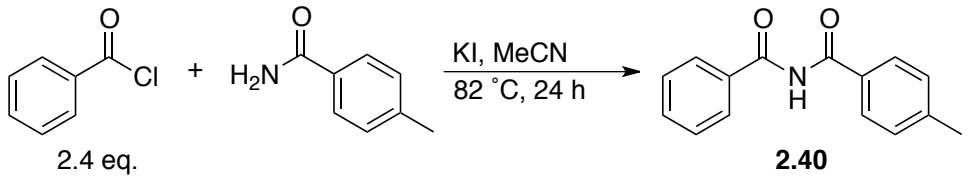
Entry	KI (mol%)[a]	Imide **2.40** conversion[b] (%)
1	0	15
2	1	11
3	2	11
4	5	16
5	10	17
6	20	14
7	30	24
8	40	16
9	50	22
10	60	48
11	70	39
12	80	40
13	90	42
14	100	34
15	150	51
16	200	49

Table 2.17. [a] Reactions were performed on a 1 mmol scale, using 1.2 mmol of acid chloride in 1 mL solvent. [b]Conversions determined by analysis of the ^{1}H NMR spectra using 2,5-dimethylfuran as an internal standard.

In a similar manner to sulfonamides the lowest mol% of potassium iodide that achieves the best conversion into imide **2.40** is 60 mol% (Table 2.17, entry 10). However, in contrast to sulfonamides an increase in potassium iodide is not detrimental to the conversion into imide, although there is no significant increase in conversion either. It was therefore necessary to look at other variables to try to optimize the imide reaction.

Increasing the temperature to 115 ˚C using butyronitrile as the solvent reduced the conversion to 18%, probably owing to either the dryness of solvent or the solubility of potassium iodide. Having seen from the solvent screen in Table 2.9 that solubility appears to be crucial to the iodide activation.

Next the amount of acid chloride was increased, the aim being to try to generate more of the suspected acid iodide intermediate, thereby increasing the concentration of electrophile and pushing the reaction towards completion, Table 2.18.



2.4 eq. **2.40**

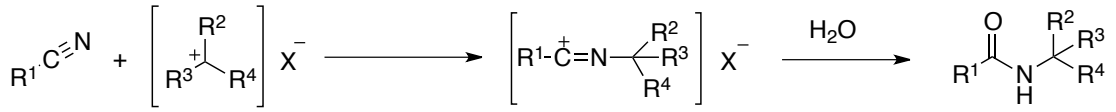
Entry	KI[a] (mol%)	Imide **2.40** conversion[b] (%)
1	0	12
2	60	50
3	120	87

Table 2.18. [a] Reactions were performed on a 1 mmol scale, using 2.4 mmol of acid chloride in 1 mL solvent. [b]Conversions determined by analysis of the ^{1}H NMR spectra using 2,5-dimethylfuran as an internal standard.

Although increasing the concentration of benzoyl chloride in itself did not increase the conversion into imide **2.40**, when the concentration of potassium iodide is doubled as well the conversion is 87% (Table 2.18, entry 3). It was noted from the results gathered so far that the best conversions, irrespective of nucleophile, are obtained when the acid chloride to potassium iodide ratio is 2:1.

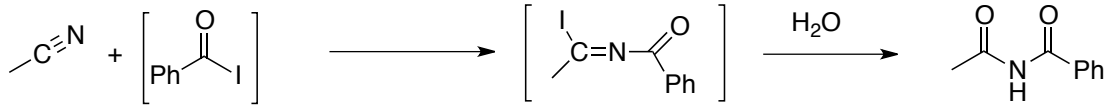
However, quantitative conversion could not be obtained for the acylation of amides. In the ^{1}H NMR a side product was observed, upon careful analysis it was deduced to be *N*-acetylbenzamide (compound **2.41**). It is possible that the solvent MeCN was

acting as nucleophile that competes with *p*-toluamide in this reaction in a 'Ritter reaction' fashion, Scheme 2.10 shows the typical Ritter reaction.



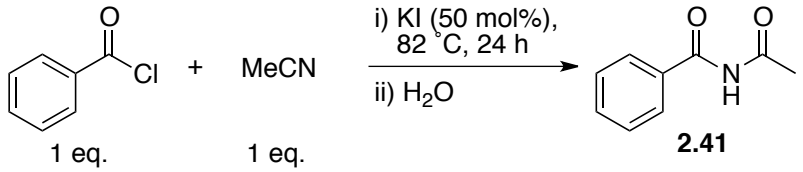
Scheme 2.10

It was hypothesized that the nitrile attacks the extremely electrophilic benzoyl iodide and that the workup procedure used might hydrolyze the intermediate and form *N*-acetylbenzamide (compound **2.41**).



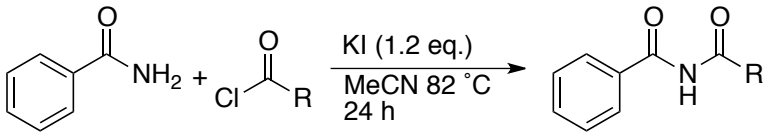
Scheme 2.11

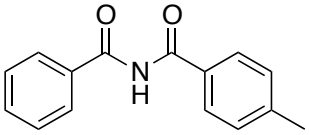
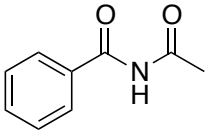
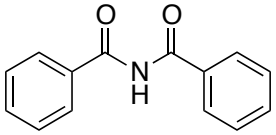
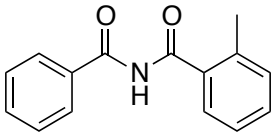
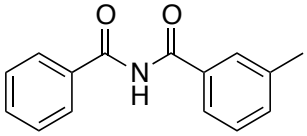
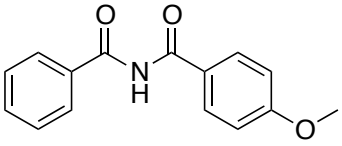
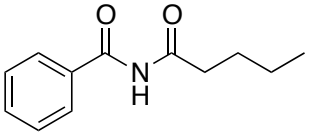
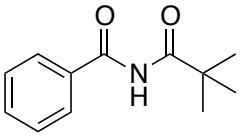
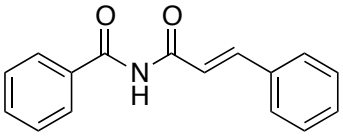
To confirm if Scheme 2.11 was a competing pathway in the acylation of amides, the reaction is run in the absence of an amide nucleophile.



Scheme 2.12

After an aqueous workup, 5% conversion into compound **2.41** is observed. This was potentially sufficient to prevent quantitative acylation of amides. However, in the presence of a better nucleophile, such as a sulfonamide, the competing pathway appears to not be so much of a factor. Optimized conditions for potassium iodide are 1.2 equivalents of potassium iodide and 2.4 equivalents of acid chloride, which is required to push the acylation near to completion. The scope of the reaction is shown below in Table 2.19 and 2.20.



Entry	Compound[a]	Imide	Conversion[b] (%)
1	**2.40**		100
2	**2.41**		100
2	**2.42**		100
3	**2.43**		100
4	**2.44**		100
5	**2.45**		58
6	**2.46**		100
7	**2.47**		66
8	**2.48**		48

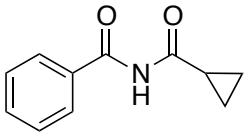
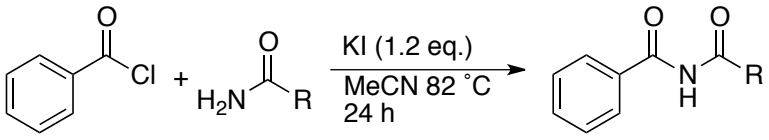
9	**2.49**		58

Table 2.19. [a]Reactions were performed on a 5 mmol scale, using 12 mmol of acid chloride in 3 mL solvent. [b]Conversions determined by analysis of the ^{1}H NMR spectra using 2,5-dimethylfuran as an internal standard.

Table 2.19 shows that quantitative conversions can be obtained with most aromatic acid chlorides, however, the factors that affect electrophilicity directly correlate to the % conversion observed, for example the 4-methoxybenzoyl chloride is an electron rich aromatic acid chloride and the electron density reduces the δ^+ on the carbonyl carbon, hence reducing electrophilicity and the observed % conversion is 58% (Table 2.19, entry 5). Table 2.20 shows the varying the electronic and steric nature of the nucleophile, the structure of the imide product means that either electrophile or nucleophile can be interchanged, depending on which is more easily available.



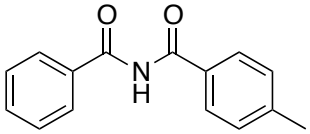
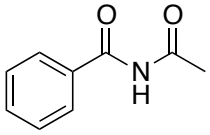
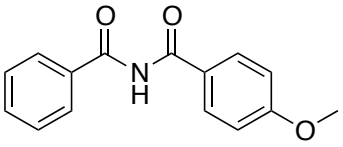
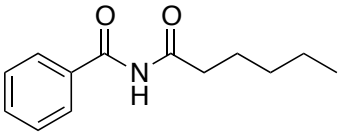
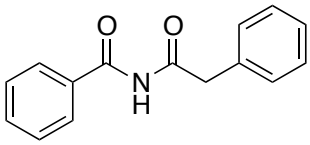
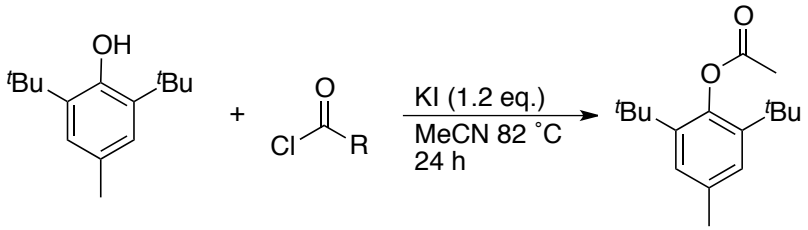
Entry	Compound[a]	Imide	Conversion[b] (%)
1	**2.40**		79
2	**2.41**		66
2	**2.50**		70
3	**2.51**		75
4	**2.52**		80

Table 2.20. [a]Reactions were performed on a 5 mmol scale, using 12 mmol of acid chloride in 3 mL solvent. [b]Conversions determined by analysis of the ^{1}H NMR spectra using 2,5-dimethylfuran as an internal standard.

Table 2.19 & 2.20 taken together show that the electrophilicity of the acid chloride is seen to determine the % conversion that can be achieved. Table 2.20 shows that the electronic and steric nature of the nucleophile has little effect on the % conversion observed. The range of % conversions is only 66-80%. Whereas in contrast when the electrophile is varied a range of % conversions of 48-100% is observed. This is an indicator that the nature of the electrophile is possibly important to the rate-determining step in the reaction. This might indicate that if the formation of acid iodide is in the reaction pathway then the formation of acid iodide might be the rate determining step. This will be considered further in the mechanism section (Section 2.4).

2.3.3 Other nucleophiles

Other nucleophiles are now considered using the optimized conditions for potassium iodide. BHT is added to various acid chlorides and the results are summarized in Table 2.21. 2.4 equivalents of acid chloride and 1.2 equivalents of potassium iodide are required to achieve the isolated yields, this probably owing, as discussed in the amide section, to the increased amount of *in situ* acid iodide generated providing more opportunities for the poor nucleophile, BHT, to attack.



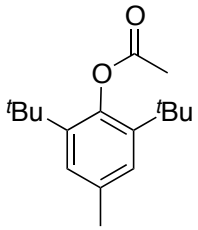
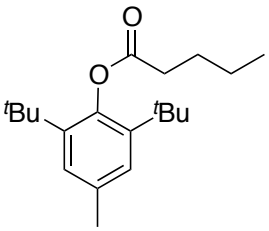
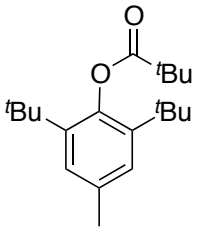
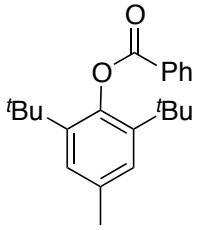
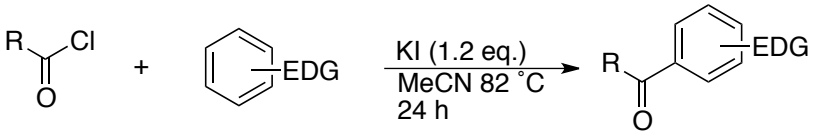
Entry	Compound[a]	*N*-Acylsulfonamide	Yield[b] (%)
1	**2.53**		95
2	**2.54**		97
3	**2.55**		54
4	**2.56**		52

Table 2.21. [a]Reactions were performed on a 3 mmol scale, using 7.2 mmol of acid chloride in 3 mL solvent. [b]Isolated yields, products purified by column chromatography.

Benzoyl chloride (Table 2.21, entry 3) and pivaloyl chloride (Table 2.21, entry 4) are poorer electrophiles than the simple aliphatic acid chlorides and as such the isolated yields shown in Table 2.21 follow the expected trend of reactivity.

Friedel-Crafts *C*-acylation of aromatic compounds was also investigated and the results are shown in Table 2.22. Electron rich aromatic compounds are necessary for acylation to occur, however there is evidence of potassium iodide activation over the background rate as shown here (Table 2.22, entry 4).



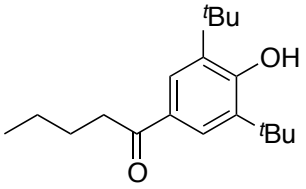
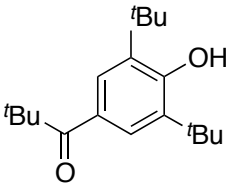
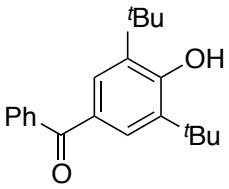
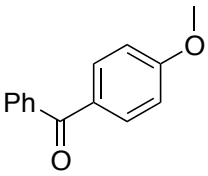
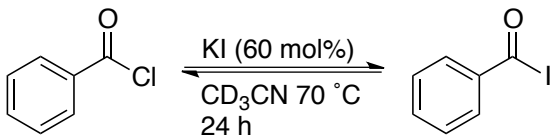
Entry	Compound[a]	*N*-Acylsulfonamide	Yield[b] (%)
1	**2.57**		97
2	**2.58**		58
3	**2.59**		30
4	**2.60**		36[c](0)

Table 2.22. [a]Reactions were performed on a 3 mmol scale, using 7.2 mmol of acid chloride in 3 mL solvent. [b]Isolated yields, products purified by column chromatography. [c]Conversion determined by analysis of the ^{1}H NMR spectra using 2,5-dimethylfuran as an internal standard.

2.4 Mechanistic investigations

^{13}C NMR experiments were carried out to provide insight into the mechanism of potassium and lithium iodide activation of acid chlorides.



2.61

Scheme 2.13

The reaction between *p*-toluenesulfonamide and benzoyl chloride with and without potassium iodide was followed by NMR analysis using CD_3CN as the solvent, Scheme 2.13. The reaction was run at a temperature of 70 ˚C because heating the solvent to reflux could be damaging to the NMR machine. Therefore the following data are not truly representative of the experimental observations that would be obtained at 82 ˚C. However, the ^{13}C NMR experiments allow us to follow the course of the reaction and potentially observe any intermediates in the process.

Initially potassium iodide was added to an NMR tube and dissolved in CD_3CN and the NMR probe pre-warmed to 70 ˚C. Benzoyl chloride is then added and the NMR tube quickly returned to the NMR machine and spectra were taken every 20 minutes for the next 24 hours. This experiment is designed to see if benzoyl iodide is formed *in situ* in the absence of a nucleophile. From the literature it is known that the ^{13}C carbonyl shift in benzoyl iodide occurs at 159.6 ppm, which compares with a shift of 168.6 ppm for benzoyl chloride.[100]

It was pleasing that a peak at 159.6 ppm appeared during the course of the experiment. Since the amount of material in the NMR tube is finite it is possible that a relative integration of the ^{13}C NMR spectrum could be used to estimate the relative % conversion of benzoyl chloride into benzoyl iodide, by comparing the respective carbonyl peaks.

The following graph shows the progress of the reaction described and depicts the formation of benzoyl iodide with time. Given the apparent error with % conversions only qualitative information can reliably be taken from the graph, however, it was approximated that an equilibrium between benzoyl iodide and benzoyl chloride is established within the first few hours of the reaction and that ~20% is the equilibrium amount of benzoyl iodide.

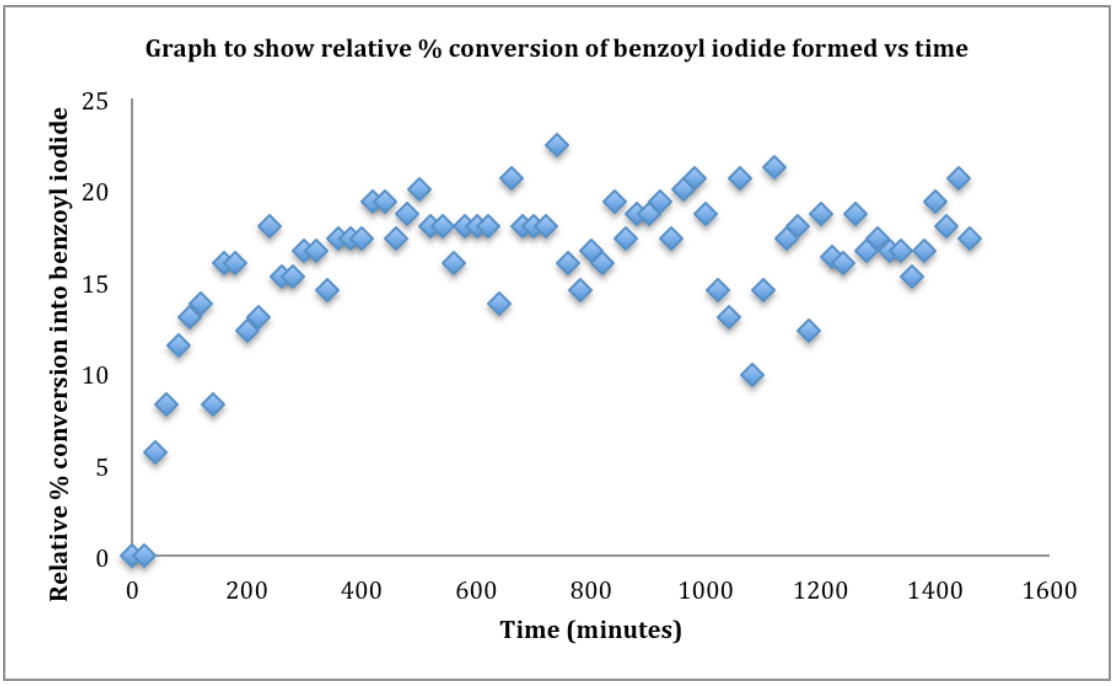


Figure 2.1

Figure 2.2 shows the initial and final ^{13}C NMR spectra for the reaction detailed in Scheme 2.13, they correspond to the first and last point on the graph in Figure 2.1. The spectra clearly demonstrate the absence and presence of the benzoyl iodide carbonyl carbon peak at 159.6 ppm. Spectrum 2 is the initial ^{13}C NMR at t = 0, spectrum 1 is the final ^{13}C NMR at t = 24 h.

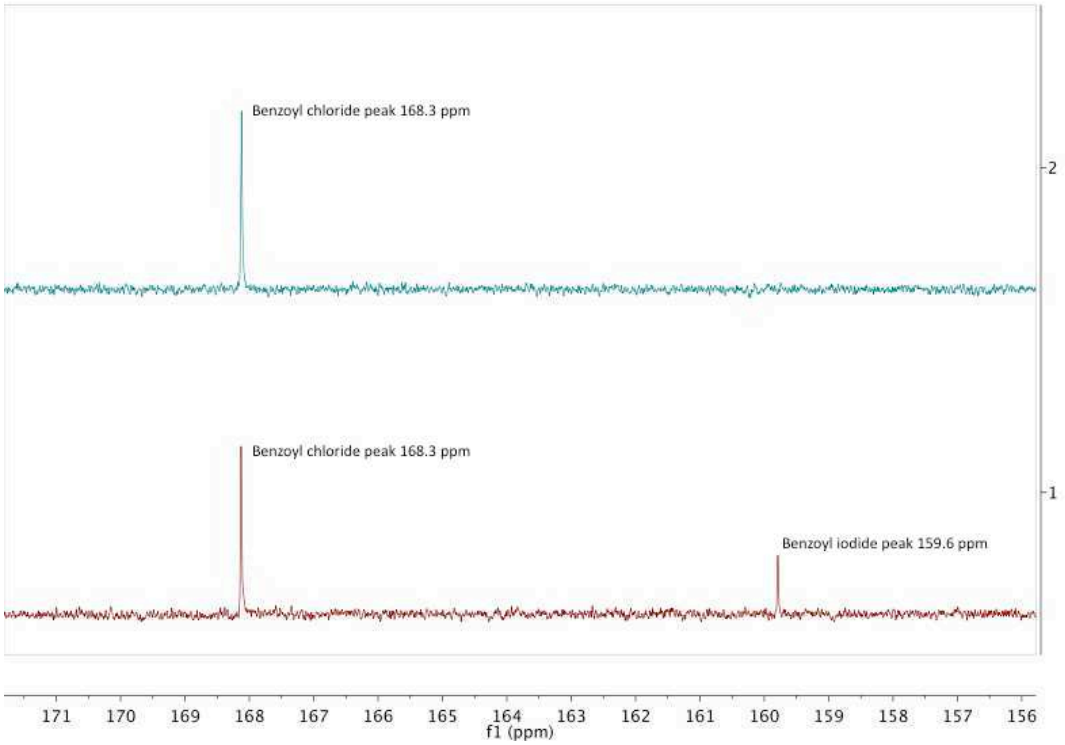
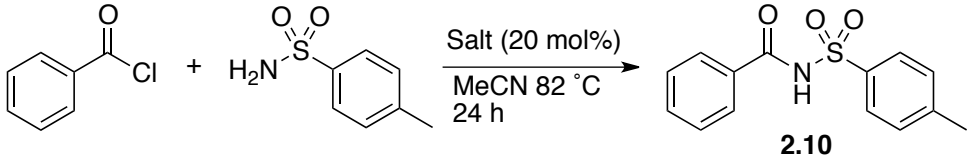


Figure 2.2

The appearance of the peak at 159.6 ppm in the ^{13}C NMR spectrum supports the idea that the acid iodide is the intermediate in the reaction.

In order to determine if the formation of acid iodide caused the increase in reactivity a further ^{13}C NMR experiment was carried out, using tetrabutylammonium iodide as the iodide source. Analysis of the ^{13}C NMR spectra showed that no benzoyl iodide formed *in situ*, with only benzoyl chloride being detected. It was seen earlier that tetrabutylammonium iodide gave 10% conversion (Table 2.11, entry 8) into the *N*-acylsulfonamide product, compared with potassium iodide, which gave 69% conversion (Table 2.11, entry 4). It was therefore assumed that potassium is necessary for the formation of acid iodide.

Other potassium and sodium salts are considered to see if acid iodide formation is necessary for acylation of sulfonamides.



2.10

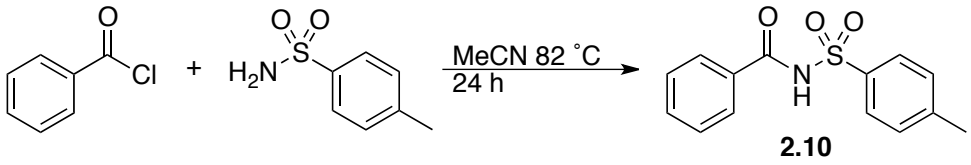
Entry	Salt[a]	*N*-Acylsulfonamide **2.10** conversion[b] (%)
1	No salt	7
2	KI	72
3	KBr	44
4	KCl	8
5	NaCl	41

Table 2.23. [a] Reactions were performed on a 1 mmol scale, using 1.2 mmol of acid chloride in 1 mL solvent. [b]Conversions determined by analysis of the ^{1}H NMR spectra using 2,5-dimethylfuran as an internal standard.

The trend down the halogen series shows that the halogen component is important in the mechanism of this reaction. This suggests that the reaction is not occurring purely by a Lewis acid mechanism.

To reinforce that the reaction is not proceeding via a Lewis acid mechanism, *p*-toluenesulfonamide and benzoyl chloride were reacted using potassium iodide in the presence of crown ethers known to sequester the potassium ion, thereby eliminating the Lewis acid mechanism pathway.[101]

The results show that potassium is successfully sequestered by both 15-crown-5 and 18-crown-6 ether. A ^{13}C NMR experiment using benzoyl chloride, potassium iodide and the crown ethers was also carried out and in the absence of a nucleophile only benzoyl chloride could be observed, no benzoyl iodide was formed. This indicates that potassium is important in the formation of the acid iodide and in turn the results in Table 2.24 show that this is crucial for the enhanced reactivity towards nucleophilic attack.



2.10

Entry	Conditions[a]	*N*-Acylsulfonamide **2.10** conversion[b] (%)
1	No salt	13
2	KI (60 mol%)	100
3	KI (60 mol%) & 15-Crown-5 ether[c]	8
4	KI (60 mol%) & 18-Crown-6 ether[c]	7

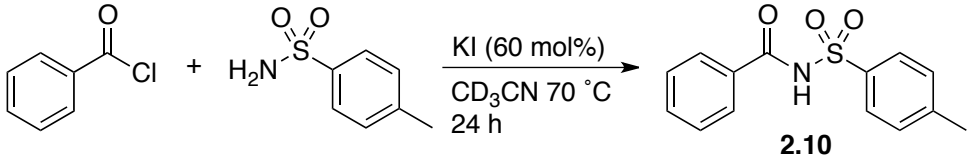
Table 2.24. [a] Reactions were performed on a 1 mmol scale, using 1.2 mmol of acid chloride in 1 mL solvent. [b]Conversions determined by analysis of the ^{1}H NMR spectra using 2,5-dimethylfuran as an internal standard. [c]2.2 equivalents of crown ether are used relative to KI, therefore 1.32 mmol.

The formation of acid iodide would enhance reactivity since acid iodides are considerably more reactive than acid chlorides. Given the greater electronegativity of chlorine over iodine it is not necessarily obvious why the acid iodide is inherently more reactive. It is reasonable to suggest that the acid iodide is more reactive owing to its greater polarizability and the fact that the lone pairs on the iodine are less able to overlap with π* (C=O).

In order to confirm the increased reactivity of an acid iodide over the acid chloride a competition experiment was carried out in an NMR machine. First the reaction shown in Scheme 2.13 was repeated. The acid chloride to acid iodide equilibrium was established, by heating the mixture for three hours, ^{13}C NMR spectra are taken to confirm the presence of benzoyl iodide, ~20%.

Secondly the NMR tube was removed from the NMR machine and 20 mol% benzylamine, a relatively good nucleophile, was added. The tube was returned to the machine and a spectrum taken immediately. The spectrum showed that there was no benzoyl iodide present, only benzoyl chloride, it also confirmed the formation of *N*-benzylbenzamide as expected. This implies that benzoyl iodide reacts preferentially with nucleophilic benzylamine.

The final ^{13}C NMR experiment carried out was to see if benzoyl iodide could be observed in the presence of *p*-toluenesulfonamide.



2.10

Scheme 2.14

For the first 24 hours of the reaction, Scheme 2.14, no benzoyl iodide peak was observed, however the reaction was followed for several hours after all the sulfonamide had been acylated. Given that an excess of benzoyl chloride is used in the reaction (1.2 eq.) it was no surprise that after three hours benzoyl iodide could be observed in the NMR spectra. This implied that as soon as benzoyl iodide was formed it underwent nucleophilic attack from the sulfonamide.

It seems reasonable to conclude that the rate determining step is the slow formation of acid iodide by reaction of acid chloride with potassium iodide. Although iodide is an excellent nucleophile in S_N2 reactions, this is not the case for addition to the carbonyl group. The difference has been attributed to the hard nature of a sp^2 carbonyl carbon compared with the relatively soft nature of the sp^3 carbon, therefore soft nucleophiles such as iodide are more effective at soft carbon sites.[102]

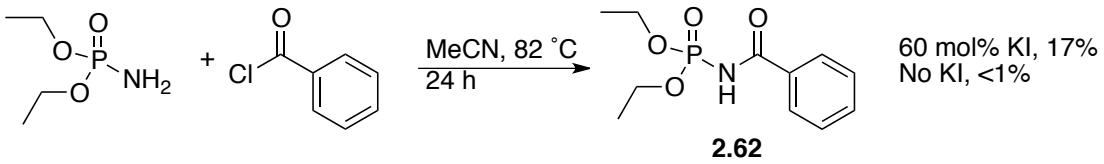
2.5 Conclusions

A synthetically useful approach to activating acid chlorides via a proposed *in situ* acid iodide intermediate has been developed, using readily available sodium or potassium iodide. This has allowed poor nucleophiles to be acylated in good to excellent yields, sometimes using a substoichiometric amount of a group I iodide.

The mechanism of iodide activated acylations has been investigated using ^{13}C NMR experiments. It has bee demonstrated that the acid iodide formation is probably the rate determining step and that potassium is essential for the formation of acid iodide *in situ*. It has also been shown that the mechanism does not follow a purely Lewis acid pathway.

2.6 Future work

Many other nucleophiles could be considered. Hindered anilines should be investigated, owing to the industrial importance of the amide products. Two further reactions were investigated in this work, however insufficient work has been carried thus far owing to time limitations and therefore these deserve further work.

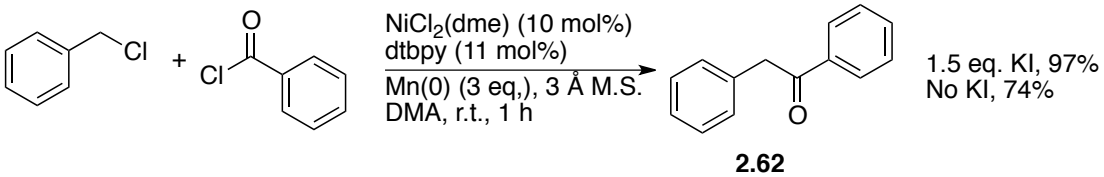


2.62

Scheme 2.15

Phosphoramidates are relatively poor nitrogen nucleophiles, for similar reasons to sulfonamides, therefore the difference between the potassium iodide activated and the unactivated conversion into compound **2.62** warrants further investigation.

The nickel catalyzed, cross coupling of acid chloride and benzyl chloride has recently been investigated by the Reisman group.[103] It is proposed that the use of the Reisman group's conditions with the addition of potassium iodide might enhance the rate of this reaction. The existing method takes 24 hours to achieve quantitative conversion. The addition of potassium iodide reduced the reaction time to just 1 hour. It was assumed that the rate enhancement came from the S_N2 reaction of iodide with benzyl chloride thereby improving the oxidative addition to the nickel complex in the cross coupling mechanism. However, further investigations could be carried out to determine if this is indeed the case or if benzoyl iodide is actually formed as well.



2.62

Scheme 2.16

Results and Discussion II

Asymmetric Transfer Hydrogenation (ATH) using 1,4-butanediol or *cis*-1,4-butenediol as a Hydrogen Source

"Alternative Hydrogen Sources for Asymmetric Transfer Hydrogenation in the Reduction of Ketones"

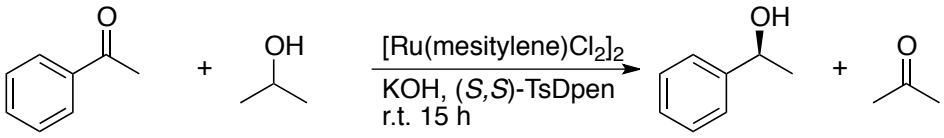
Wakeham, R. J.; Morris, J. A.; Williams, J. M. J., *Chem. Eur. J.* **2014,** submitted

Asymmetric Transfer Hydrogenation (ATH) using 1,4-butanediol or *cis*-1,4-butenediol as a Hydrogen Source

Chapter 3: Results and Discussion II

3.1 Aims

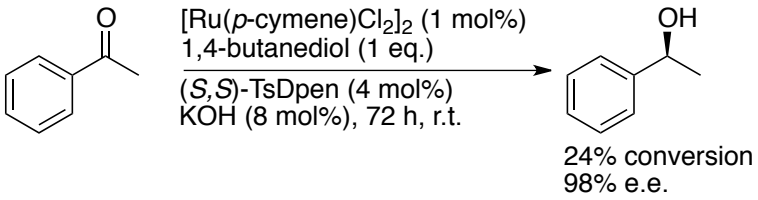
The aim of this work was to investigate the use of alternative hydrogen sources for asymmetric transfer hydrogenation (ATH) in the reduction of ketones.



Scheme 3.1[104]

The reaction shown in Scheme 3.1 was part of *Noyori's* earliest work into catalytic asymmetric transfer hydrogenation. This reaction used IPA as the hydrogen source. However, for every molecule of IPA that was oxidized to acetone, a ketone was produced that more easily reduced by the catalyst than the substrate ketone. Therefore a large excess of IPA was used to drive the reaction near completion. In the reaction shown in Scheme 3.1 the ruthenium pre-catalyst, ligand ((*S,S*)-TsDpen) and IPA were initially heated to 80 ˚C to form the active catalyst before the substrate ketone was added diluted in IPA.

Previous work in the group has shown 1,4-butanediol to be an effective hydrogen source,[105] the mechanism for this will be discussed later in the chapter. However, optimizing the reaction for the asymmetric reduction of ketones had not been possible. Previously only high yield with low enantiomeric excess or low yield with high enantiomeric excess, has been achieved.

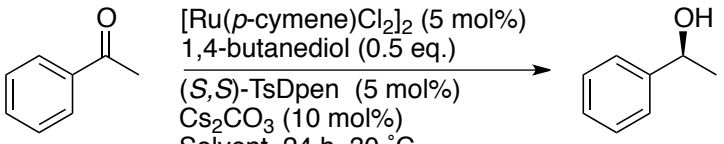


Scheme 3.2

Further investigations into this reaction were undertaken and form the basis of this work.

3.2 Initial work

Initially similar conditions to those shown in Scheme 3.2 were taken. It was of interest to determine if the use of solvent would increase the conversion and retain the selectivity previously observed.

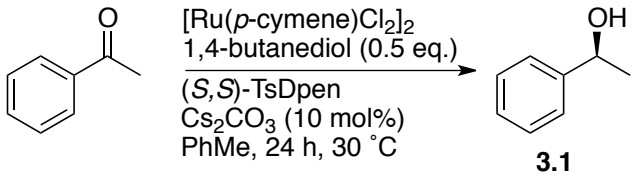


3.1

Entry	Solvent[a]	Alcohol **3.1** % conversion[b] (% e.e.)[c]
1	DCM	45(91)
2	THF	38(>99)
3	Et_2O	49(89)
4	PhMe	52(>99)
5	MeCN	46(90)
6	Hexane	31(89)
7	^{t}BuOH	17(97)

Table 3.1. [a]Reactions were performed on a 1 mmol scale in 1 mL solvent. [b]Conversions determined by analysis of the ^{1}H NMR spectra. [c]Enantiomeric excess calculated using HPLC after purification by column chromatography.

It was found that PhMe provided the best result under these conditions (Table 3.1, entry 4). The catalyst and ligand loading were considered, using toluene as the solvent, with the intention of increasing the % conversion into alcohol **3.1** whilst retaining the enantioselectivity.



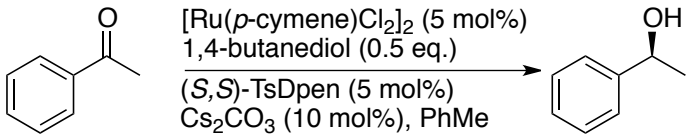
3.1

Entry	Catalyst[a] (mol%)	Ligand[b] (mol%)	Alcohol **3.1** % conversion[c] (% e.e.)[d]
1	1	1	58(92)
2	1	2	43(92)
3	2	2	61(81)
4	2	4	41(93)
5	3	3	44(89)
6	3	6	53(89)
7	4	4	39(91)
8	4	8	56(84)
9	5	5	27(95)
10	5	10	32(94)

Table 3.2. [a]Reactions were performed on a 1 mmol scale in 1 mL solvent, catalyst is [Ru(*p*-cymene)Cl_2]$_2$. [b]Ligand is (*S,S*)-TsDpen . [c]Conversions determined by analysis of the ^{1}H NMR spectra. [d]Enantiomeric excess calculated using HPLC after purification by column chromatography.

The results in Table 3.2 showed that the amount of catalyst and ligand has little effect on the overall conversion and enantioselectivity. This was counter-intuitive and indicated that there might have been an issue with obtaining consistent results.

Further inconsistencies were observed when the reaction time and temperature were varied. When the temperature was reduced to 30 ˚C the conversion over 72 h was 56% in 0.25 mL of solvent and 58% in 1 mL solvent (Table 3.3, entries 6 & 7). Two other experiments were also run with 0.5 & 0.75 mL of solvent however <5% conversion was obtained. It was deduced that the careful mixing of the reagents was necessary for the reaction to proceed and as such the conversions obtained thus far were unreliable. Table 3.3 also shows that after 24 h at 40 ˚C the reaction proceeds to 72% conversion however the enantioselectivity was reduced to 72% e.e. (Table 3.3, entry 5) indicating that extended reaction times led to reduced e.e.



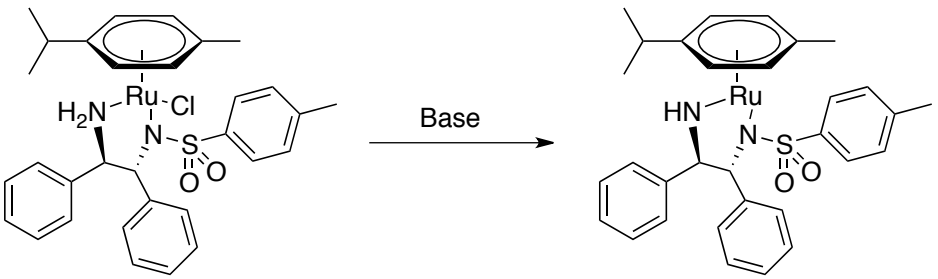
3.1

Entry	Time[a] (h)	Alcohol **3.1** % conversion[b] (% e.e.)[c]
1	1	32(>99)
2	1[d]	41(>99)
3	2	48(>99)
4	4	29(95)
5	24	72(72)
6	72[e]	58(>99)
7	72[e,f]	56(>99)

Table 3.3. [a]Reactions were performed on a 1 mmol scale in 1 mL solvent at 40 ˚C. [b]Conversions determined by analysis of the ^{1}H NMR spectra. [c]Enantiomeric excess calculated using HPLC after purification by column chromatography. [d]Reaction performed at 50 ˚C. [e]Reaction performed at 30 ˚C. [f]Reaction perfomed on a 1 mmol scale in 0.25 mL solvent.

The erratic results obtained were attributed to mixing issues possibly caused by the viscosity of 1,4-butanediol. The careful addition of reagents and the use of identical stirrer bars, that were tested to check that mixing of the reagents was good, were used in subsequent experiments.

Next the choice of base was investigated, the role of base is to activate the catalyst as shown in Scheme 3.3. The pre-catalyst **3.2** is activated to the true catalyst **3.3** by elimination of HCl. The 16e complex, **3.3** is a characteristic purple colour in solution.

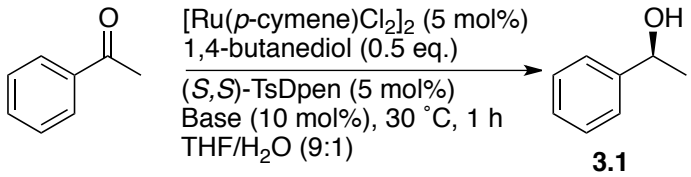


3.2 **3.3**

Scheme 3.3

Focusing on the % conversion, DBU gave a conversion of 21% and KO^{t}Bu gave 29% so they showed no improvement over Cs_2CO_3. Next the use of sodium hydride was tested and the pre-catalyst formation before addition of the substrates was attempted but this resulted in no conversion.

It was hypothesized that the solubility of base in toluene might be causing an issue with the activation of the catalyst, which, in turn resulted in lower conversions. Since it had previously been seen that THF could be a good alternative to toluene (Table 3.1, entry 2) THF was investigated further. The main advantage of THF was its miscibility with water, which allowed the base to dissolve in a THF water mix, resulting in a homogeneous solution. A screen bases was carried out in the 9:1 THF/H_2O solvent, shown in Table 3.4.

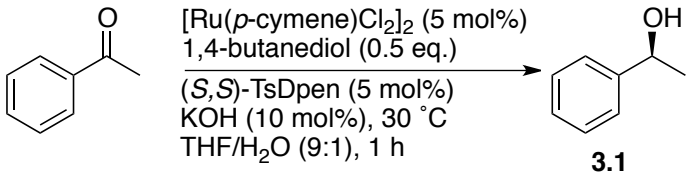


3.1

Entry	Base[a]	Alcohol **3.1** % conversion[b] (% e.e.)[c]
1	K_2CO_3	26(95)
2	LiOH	21(>99)
3	NaOH	49(89)
4	KOH	36(>99)

Table 3.4. [a]Reactions were performed on a 1 mmol scale in 0.5 mL solvent. [b]Conversions determined by analysis of the ^{1}H NMR spectra. [c]Enantiomeric excess calculated using HPLC after purification by column chromatography.

It was hoped that the homogeneous solution, careful addition of reagents and careful selection of stirrer bar would provide more consistent results. The results show that the best base for activation of the catalyst was KOH (Table 3.4, entry 4). However, when it was carried out three similtaneous reactions with identical reagents and under identical conditions identical results were not observed.



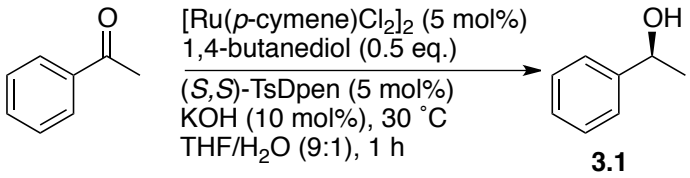
3.1

Entry[a]	Alcohol **3.1** % conversion[b]
1	22(32)
2	13(29)
3	11(5)

Table 3.5. [a]Reactions were performed on a 1 mmol scale in 0.5 mL solvent. [b]Conversions determined by analysis of the ^{1}H NMR spectra from a sample of the reaction mixture, figures in parenthesis are conversions determined after 2 h reaction time.

The results showed that unless the mixing of reagents is perfect then the reduction can fail to start as in the case of entry 3**,** Table 3.5.

The amount of base to optimize the reaction further was investigated. Noyori's system required 5 equivalents of base to ruthenium. It was observed that 30 mol% KOH gave the best conversion with the highest enantiomeric excess (Table 3.6, entry 4).

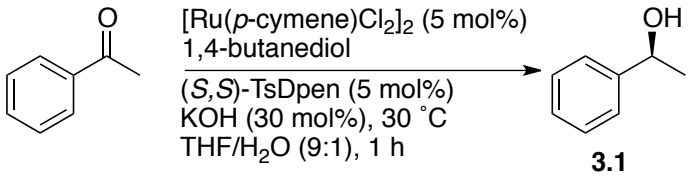


3.1

Entry	KOH[a] (mol%)	Alcohol **3.1** % conversion[b] (% e.e.)[c]
1	5	7(-)
2	10	32(94)
3	20	28(>99)
4	30	37(>99)
5	40	38(92)
6	50	27(>99)
7	110	31(>99)

Table 3.6. [a]Reactions were performed on a 1 mmol scale in 0.5 mL solvent. [b]Conversions determined by analysis of the ^{1}H NMR spectra. [c]Enantiomeric excess calculated using HPLC after purification by column chromatography.

Raising the amount of 1,4-butanediol was investigated to increase the amount of available hydrogen to try to increase the reduction of the acetophenone into 1-phenylethanol **3.1.**

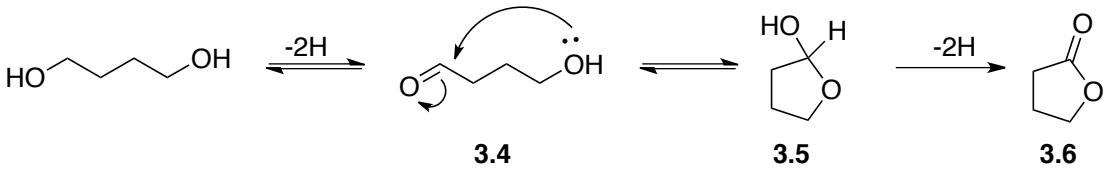


3.1

Entry	1,4-butanediol[a] (eq.)	Alcohol **3.1** % conversion[b]
1	2	46
2	3	52
3	4	53
4	5	53
5	10	49

Table 3.7. [a]Reactions were performed on a 1 mmol scale in 0.5 mL solvent. [b]Conversions determined by analysis of the ^{1}H NMR spectra.

The results in Table 3.7 show that increasing the amount of hydrogen source available does not alter the rate of reduction of ketone. Below in Scheme 3.4 the possible mechanism for 1,4-butanediol as a hydrogen source is shown.



3.4 **3.5** **3.6**

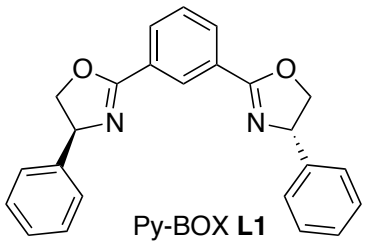
Scheme 3.4

The advantage of using 1,4-butanediol over IPA should be the final irrevesible step which means that the γ-butyrolactone product **3.6** is stable with respect to the reverse reduction step. This eliminates the equilibrium problem associated with IPA. However, from the results it was seen that the use of 0.5 equivalents 1,4-butanediol has not resulted in quantitative conversion as the theory suggests it should. Therefore the reduction of acetophenone in the presence of half an equivalent of γ-butyrolactone was tested. The conversion of acetophenone into alcohol **3.1** was shut down in the presence of the lactone. Therefore the lactone product **3.6** formed by the oxidation of 1,4-butanediol and subsequent oxidation of lactol **3.5** poisoned the catalyst. Therefore as the reaction progressed the turnover of the catalyst was retarded and full reduction of acetophenone was not possible.

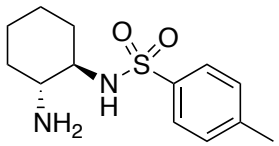
Interestingly because KOH was used as the base to activate the ruthenium catalyst **3.2**, the hydroxide ion would be able to ring open γ-butyrolactone to form the corresponding 4-hydroxybutyric acid. Therefore the reaction was carried out in the presence of a greater amount of KOH to try to prevent the lactone product poisoning the catalyst. However, this did not improve the conversion into alcohol **3.1**.

Therefore different ligands were looked at to see the effect they had on the reaction and to try to form an active catalyst that was less suceptible to poisoning by the lactone product formed. The results are summarized in Table 3.7. At this stage only

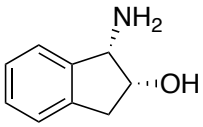
% conversion was considered to try to focus on optimizing the reaction to achieve quantitative conversion. Scheme 3.5 shows the ligands that were tested.



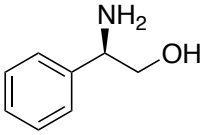
Py-BOX **L1**



TsCYDN **L2**



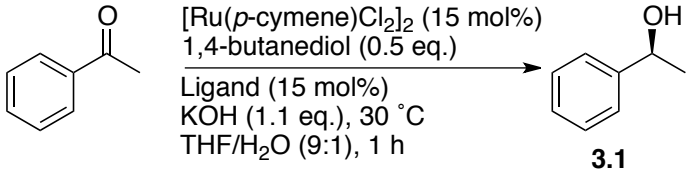
(*1S,2R*)-(-)-*cis*-1-amino-2-indanol **L3**



(*R*)-(-)-2-phenylglycinol **L4**

Scheme 3.5

The diamine, bisoxazoline and aminoalcohol ligands were considered, phosphine based ligands were not investigated and this may be an area for future work.



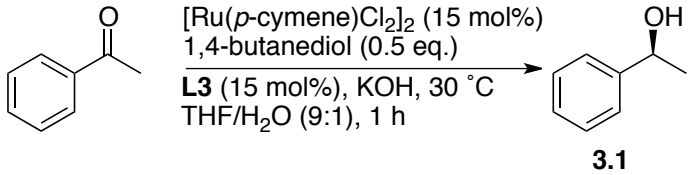
3.1

Entry	Ligand[a]	Alcohol **3.1** % conversion[b]
1	**L1**	5
2	**L2**	35
3	**L3**	76
4	**L4**	10

Table 3.8. [a]Reactions were performed on a 1 mmol scale in 0.5 mL solvent. [b]Conversions determined by analysis of the ^{1}H NMR spectra.

The aminoindanol ligand showed the best reduction of the ketone (Table 3.8, entry 2) and so optimizing the reaction further using the **L3** ligand was undertaken.

The effect of increasing the amount of base further was investigated, using more than 1.1 equivalents to see what effect that had on the reduction of the ketone.

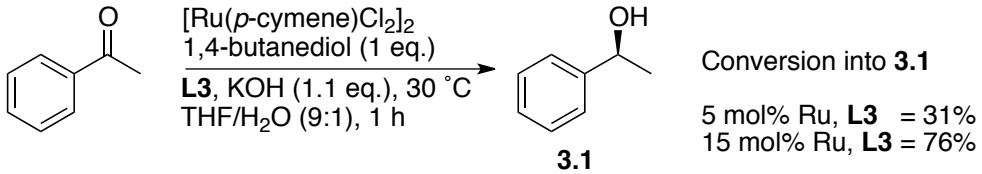


3.1

Entry	KOH[a] (eq.)	Alcohol **3.1** % conversion[b]
1	1.2	73
2	1.3	69
3	1.4	70
4	1.5	76
5	1.6	69
6	1.7	71
7	1.8	70

Table 3.9. [a]Reactions were performed on a 1 mmol scale in 0.5 mL solvent. [b]Conversions determined by analysis of the ^{1}H NMR spectra.

The results in Table 3.9 show that the amount of KOH above 1.1 equivalents has no effect on the reduction of ketone to alcohol **3.1**. Therefore increasing the amount of 1,4-butanediol was considered. When 1 equivalent of 1,4 butanediol was used and the temperature was raised to 50 ˚C, 94% conversion into **3.1** was observed. 15 mol% ruthenium was used, which was a large amount of ruthenium to use and reactions on any scale bigger than a few mmol would be very expensive. However, it was desirable to lower the catalyst loading and the temperature for the reaction.

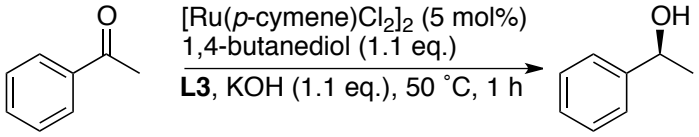


3.1

Scheme 3.6

However, as shown in Scheme 3.6 lowering the temperature reduced the conversion from 94% to 76% and lowering the amount of catalyst and ligand reduced the conversion further still to 31%.

Next a small changes in the amount of ligand, **L3** was considered, with 5 mol% ruthenium and in the absence of solvent. It was observed that 6.25 mol% **L3** (Table 3.10, entry 5) showed the best % conversion obtained so far.

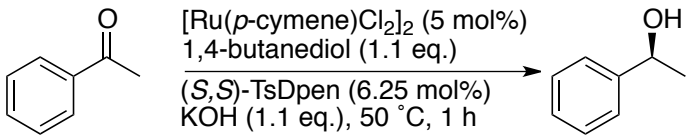


3.1

Entry	**L3**[a] (mol%)	Alcohol **3.1** % conversion[b]
1	1.25	47
2	2.50	58
3	3.75	43
4	5.00	92
5	6.25	95
6	7.50	92

Table 3.10. [a]Reactions were performed on a 1 mmol scale. [b]Conversions determined by analysis of the ^{1}H NMR spectra.

With hindsight however, it was not sensible to only focus on the % conversion since when the enantiomeric excess of entry 5, Table 3.10 was determined it was found the alcohol product **3.1** was racemic.



3.1

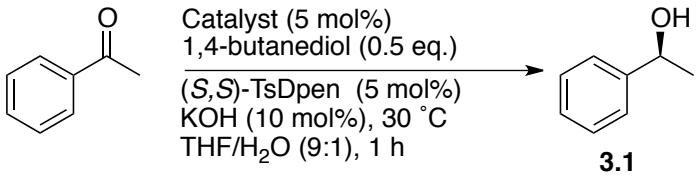
Neat: conversion = 72%, e.e.= 69%
THF/H_2O (9:1): conversion = 48%, e.e.= 90%

Scheme 3.7

Scheme 3.7 represents the best compromise of conversion and e.e. that could be achieved with dichlororuthenium(II)*p*-cymene dimer as the catalyst, (*S,S*)-TsDPEN as the ligand and 1,4-butanediol as the hydrogen source.

3.3 Other catalysts

It was hypothesized that the stability of the catalyst was affecting turnover and enantioselectivity, therefore other catalysts were screened to test their viability.



3.1

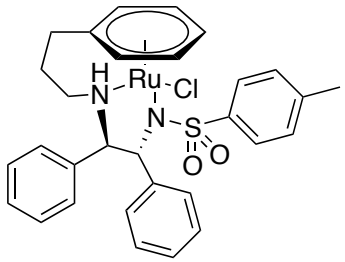
Entry	Catalyst[a]	Alcohol **3.1** % conversion[b] (% e.e.)[c]
1	$Ru(PPh_3)_3H_2CO$	0(-)
2	$[IrCp^*Cl_2]_2$	0(-)
3	$H_2IrCl_6.4H_2O$	0(-)
4	$Ru(PPh_3)_3Cl_2$	0(-)
5	$Ru(PPh_3)_3ClH(CO)$	0(-)
6	$[Ir(COD)Cl]_2$	12(90)
7	$Ir_4(CO)_{12}$	0(-)
8	$[Ru(C_6H_6)Cl_2]_2$	0(-)
9	$[Ru(C_6Me_6)Cl_2]_2$	46(0)

Table 3.11. [a]Reactions were performed on a 1 mmol scale in 1 mL solvent. [b]Conversions determined by analysis of the ^{1}H NMR spectra. [c]Enantiomeric excess calculated using HPLC after purification by column chromatography.

The results shown in Table 3.11 show that most transfer hydrogenation catalysts were ineffective under these conditions. The stability of the η^6-aromatic group on the ruthenium catalyst is important for the stability of the catalyst[88] and this increase in stability results in better conversions. When hexamethylbenzene ruthenium

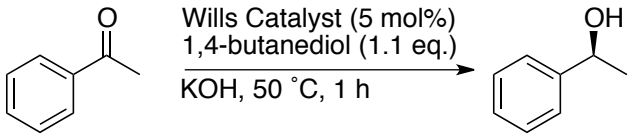
catatlyst (Table 3.11, entry 9) was used with **L3** instead of (*S,S*)-TsDPEN, 100% conversion in one hour was observed, the alcohol was again racemic.

Now the ability to reduce acetophenone fully to 1-phenylethanol in one hour was possible, however, with no stereochemical control. A catalyst that had the stability and chirality combined in one structure was desired. The tethered Wills catalyst, shown in Scheme 3.8**,** was investigated.



Scheme 3.8

The first step was to consider the effect of base on the activity of the Wills catalyst. Table 3.12 shows that the stability of the catalyst resulted in a high conversion and that base was necessary to activate the catalyst, 10 mol% was required (Table 3.12, entry 2).

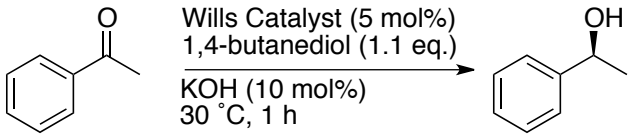


3.1

Entry	KOH[a] (mol%)	Alcohol **3.1** % conversion[b] (% e.e.)[c]
1	0	<5(-)
2	10	91(0)
3	110	90(0)

Table 3.12. [a]Reactions were performed on a 1 mmol scale. [b]Conversions determined by analysis of the ^{1}H NMR spectra. [c]Enantiomeric excess calculated using HPLC after purification by column chromatography.

The lack of stereochemical control was disappointing. Therefore running the reaction in THF was considered, since this had previously provided greater enantiomeric selectivity. Also, the temperature was lowered to try to improve selectivity further. Other solvents were shown to not improve the e.e. above what could be achieved in THF.



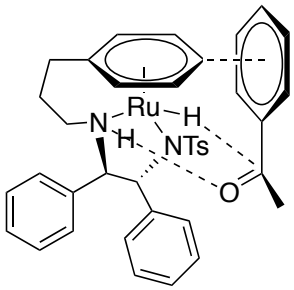
3.1

Entry	THF[a] (mL)	Alcohol **3.1** % conversion[b] (% e.e.)[c]
1	0.25	68(91)
2	0.50	78(76)
3	1.00	69(70)

Table 3.13. [a]Reactions were performed on a 1 mmol scale. [b]Conversions determined by analysis of the ^{1}H NMR spectra. [c]Enantiomeric excess calculated using HPLC after purification by column chromatography.

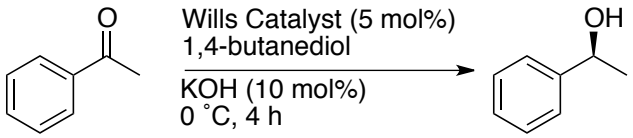
Table 3.13 shows that higher conversions were obtained with higher enantioselectivity. It was necessary to improve the figures further and so extended the reaction time and investigated increasing the amount of 1,4-butanediol. It was hypothesized that the enantioselectivity was affected by temperature and proceeded to cool the reaction to 0 ˚C to confirm this.

Shown in Scheme 3.9 is the transition state for a ketone bound to the Wills catalyst. It is widely accepted that there is an electrostatic C(sp^2)H/π-interaction between the δ^+ of the electron poor hydrogen on the ruthenium aromatic and the δ^- of the electron rich phenyl ring on the substrate ketone. This gives the catalyst its stereochemical control and this type of interaction also applys to the Noyori catalyst system.[106]



Scheme 3.9

It is this interaction that helps explain why the (*S,S*) enantiomer of the Wills catalyst gives (*S*)-1-phenylethanol in the reduction of acetophenone.



3.1

Entry	1,4-butanediol[a] (eq.)	Alcohol **3.1** % conversion[b] (% e.e.)[c]
1	1.1[d]	73(79)
2	1.1	53(89)
3	2.0[d]	96(62)
4	2.0	67(86)
5	4.0	67(86)

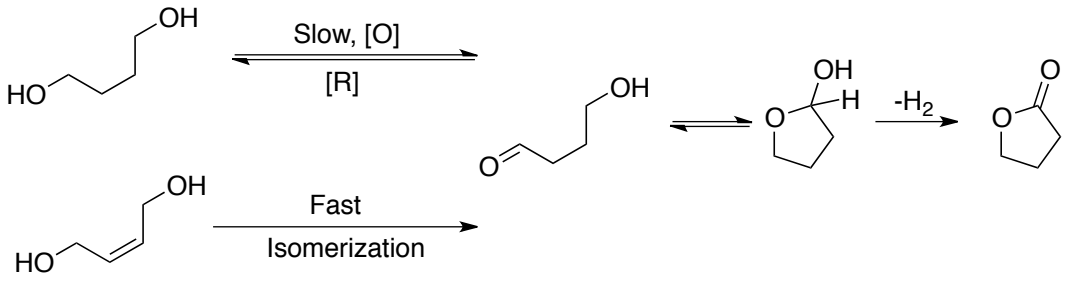
Table 3.14. [a]Reactions were performed on a 1 mmol scale in 0.25 mL solvent. [b]Conversions determined by analysis of the ^{1}H NMR spectra. [c]Enantiomeric excess calculated using HPLC after purification by column chromatography. [d]Reaction performed at 30 ˚C.

Although 67% conversion and 86% e.e. had been achieved with two equivalents of 1,4-butanediol it was disappointing that the figures could not be improved upon.

3.4 *cis*-1,4-Butenediol

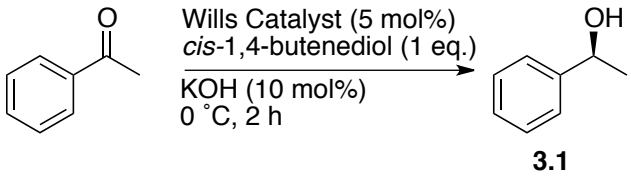
At this stage an alternative hydrogen source was considered. *cis*-1,4-Butenediol is synthesized on an industrial scale from 2-butyne-1,4-diol. It is important in the production of endosulfan,[107] Vitamins A & B[108] and is an additive in resin

manufacturing.[109] 2-butyne-1,4-diol is synthesised from the Reppe carbonylation of acetylene using formaldehyde as the carbonyl source, therefore it is cheaply produced.[110] Lindlar's catalyst[111] as well as many supported palladium[108, 112] and nickel catalysts[113] are able to hydrogenate butynediol to butenediol selectively. Therefore this was considered a suitably cheap available hydrogen source for these investigations.



Scheme 3.10

cis-1,4-Butenediol was chosen to be investigated given that the isomerisation of *cis*-1,4-butenediol to 4-hydroxybutanal is catalysed by ruthenium transfer hydrogentation catalysts.[114] Therefore if the catalyst could carry out the faster isomerisation step and then subsequently oxidise the lactol to the lactone it would demonstrate another irrevesible hydrogen source, as shown in Scheme 3.10. It is important to note that this would require twice as much diol than 1,4-butanediol given that only two hydrogens are liberated in the oxidation of lactol.



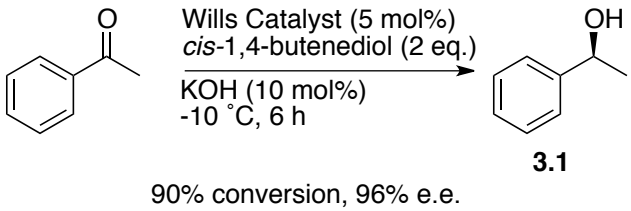
3.1

88% conversion, 94% e.e.

Scheme 3.11

Using the optimisation carried out so far, it was possible to use *cis*-1,4-butenediol to achieve 88% conversion with 94% e.e as shown in Scheme 3.11.

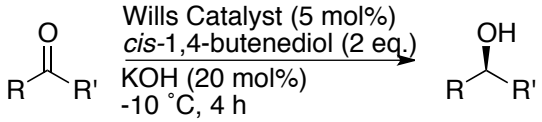
Lowering the temperature to -10 ˚C to try to improve the e.e., with two equivalents of *cis*-1,4-butenediol and extended the reaction time. Good conversion and enantiomeric excess were achieved as shown in Scheme 3.12.

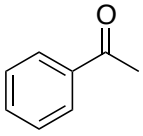
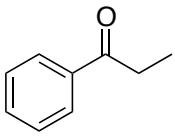


Scheme 3.12

It was noted from all the previous investigations into this transformation that longer reaction times usually resulted in a reduction in enantiomeric excess. An experiment was conducted with the conditions shown in Scheme 3.11 starting from 1-phenylethanol to measure the amount of racemization that occurs under these conditions. The enantiomerically pure (*S*)-1-phenylethanol had an e.e. of >99% and after 1 hour under the reaction conditions the e.e. was 98% demonstrating that racemization was occurring.

Then the amount of KOH was increased to 20 mol% and reduced the reaction time to finally achieve the optimal conditions. The scope of this reaction was then investigated as shown in Table 3.15.



Entry	Compound[a]	Alcohol	% Yield[b] (% e.e.)[c]
1	**3.1**		85(>99)
2	**3.7**		51[d](96)

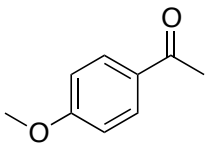
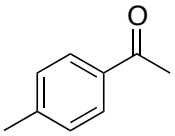
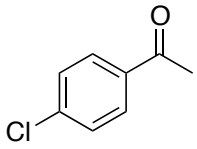
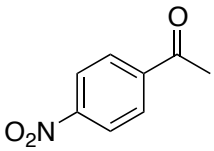
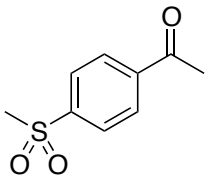
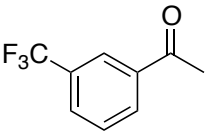
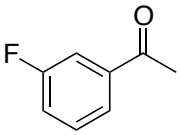
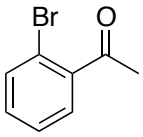
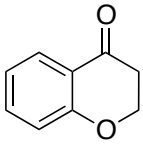
3	**3.8**		99(96)
4	**3.9**		96(>99)
5	**3.10**		93(>99)
6	**3.11**		55(86)
7	**3.12**		91(75[e])
8	**3.13**		59(93[f])
9	**3.14**		96(80[f])
10	**3.15**		89(79)
11	**3.16**		80(99)

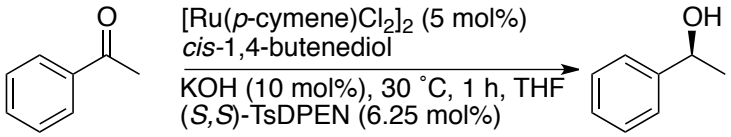
Table 3.15. [a]Reactions were performed on a 1 mmol scale in 0.25 mL solvent. [b]Conversions determined by analysis of the ^{1}H NMR spectra**.** [c]Enantiomeric excess calculated using HPLC after purification by column chromatography. [d]Reaction time 16 h. [e]Enantiomeric excess calculated using ^{1}H NMR and a chiral shift reagent. [f]Enantiomeric excess calculated using specific rotation.

Table 3.15 shows that this method was tolerant of electron rich and electron poor aromatic ketones, *ortho* and *meta* substituents were also tolerated. The method was less effective with propiophenone (Table 3.15, entry 2) which required an extended reaction time and resulted in a lower yield than for acetophenone. It is proposed that this is because the ethyl group is sufficiently disruptive to the catalyst compared with a methyl group that the turnover of the catalyst is affected by propiophenone.

Lower yields obtained for entires 8 and 6 were attributed to solubility issues when carrying out purification, since the conversion for both substrates was 100%.

3.5 *cis*-1,4-Butenediol with [Ru(*p*-cymene)Cl_2]$_2$

After successfully optimizing the ATH using Wills catalyst and *cis*-1,4-butenediol the investigations returned to the cheaper [Ru(*p*-cymene)Cl_2]$_2$ and (*S,S*)-TsDPEN catalyst system.

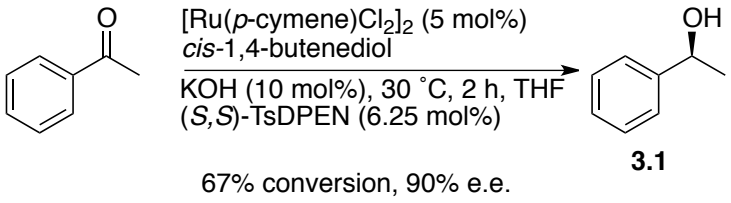


3.1

Entry	*cis*-1,4-butenediol[a] (eq.)	Alcohol **3.1** % conversion[b]
1	1.1	36
2	2.0	44
3	4.0	44

Table 3.16. [a]Reactions were performed on a 1 mmol scale in 0.25 mL solvent. [b]Conversions determined by analysis of the ^{1}H NMR spectra.

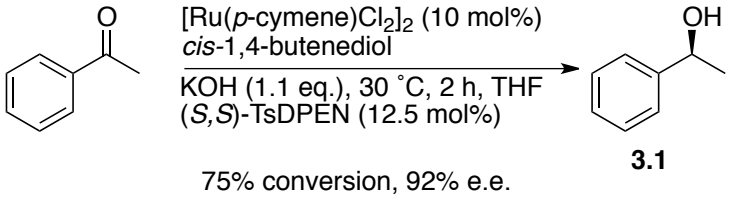
Next the slow addition of *cis*-1,4-butenediol was investigated, to allow time for the catalyst to isomerize the diol to 4-hydroxybutanal.



Scheme 3.13

Scheme 3.13 shows that when *cis*-1,4-butenediol is added at a rate of 1 mmol per 30 minutes, a reasonable conversion and enantioselectivity can be achieved with this catalyst system.

Finally, increasing the amount of catalyst and ligand and also increasing the amount of base, using slow addition of *cis*-1,4-butenediol (one mmol per 30 minutes to total four mmol over two hours) gave 75% conversion and 92% e.e.

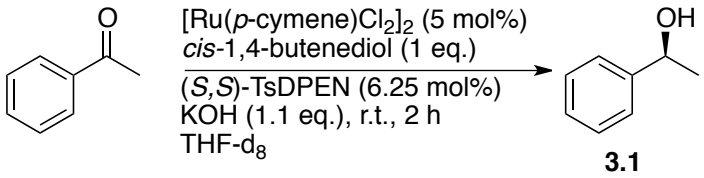


Scheme 3.14

Therefore *cis*-1,4-butenediol is a more effective hydrogen source for ATH reactions than 1,4-butanediol.

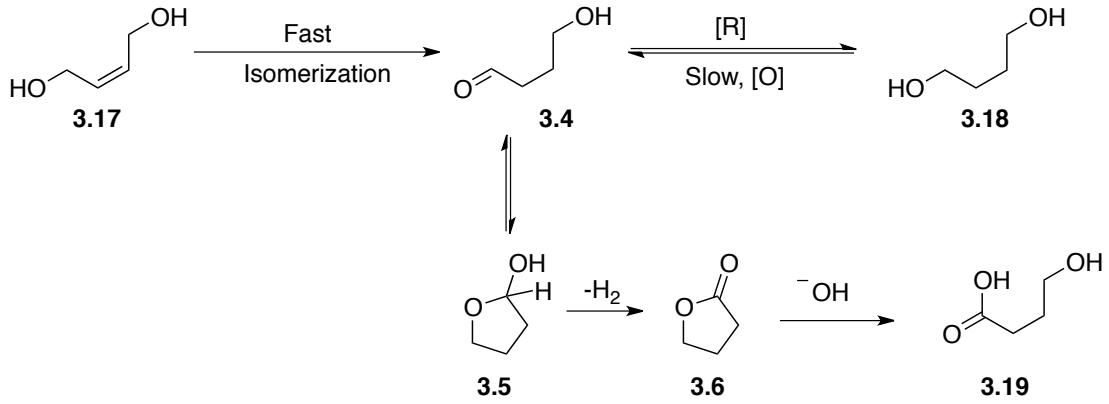
3.6 Mechanistic investigation

^{1}H NMR experiments were carried out to try to understand the mechanism by which *cis*-1,4-butenediol acts as a hydrogen source.



Scheme 3.15

Scheme 3.15 shows the conditions for the initial ^{1}H NMR experiment where in the presence of the substrate ketone, the rapid reduction of acetophenone to 1-phenylethanol and also the disappearance of the *cis*-1,4-butenediol peaks were observed. However, it was not possible to determine what *cis*-1,4-butenediol had been converted in to. It was expected that the formation of γ-butyrolactone with formation of 1-phenylethanol could be seen. However a significant amount of lactone was not observed being formed. When the same ^{1}H NMR experiment was conducted in the absence of acetopheone the disappearance of *cis*-1,4-butenediol and the formation of a small amount of γ-butyrolactone was still observed. The largest peaks in the NMR spectrum were attributed to 1,4-butanediol. This was confirmed by addition of 0.5 equivalents of 1,4-butanediol to the NMR tube and another spectrum taken and analysed. This indicates that there may be another pathway.



Scheme 3.16

One possible pathway, shown in Scheme 3.16, was that once isomerized to 4-hydroxybutanal **3.4** the aldehyde could be reduced to an alcohol **3.18** before

cyclisation to the lactol **3.5**. However, one would expect the intramolecular cyclisation to proceed more quickly than the reduction.

From the analysis of the ^{1}H NMR there was no evidence of any lactol **3.5** being formed, there was no evidence of 4-hydroxybutanal **3.4** being formed. *cis*-1,4-Butenediol **3.17** peaks were observed disappearing whilst 1,4-butanediol **3.18** peaks appeared. Unfortunately sufficient Wills catalyst was not available to carry out further ^{1}H NMR experiments to confirm that the same products were observed with the alternative catalyst.

3.7 Conclusion

It was demonstrated that 1,4-butanediol can be used as a hydrogen source for the asymmetric transfer hydrogentaion of aromatic ketones. However, the conversion and enantiomeric excess were lower than desired and since many other catalytic systems exist that can perform this transformation more efficiently this outcome was not especially satisfying.

It is possible to use *cis*-1,4-butenediol as a hydrogen source that with the ruthenium catalysts tested here, out performed 1,4-butanediol. With the use of a tethered ruthenium catalyst, Wills catalyst it was possible to reduce a range of ketones in good to excellent yields and with good to excellent enantioselectivity.

Brief mechanistic insight was gained from the NMR experiments, however it was not possible to determine an exact mechanism for the reduction of ketones. If it were possible to determine exactly how *cis*-1,4-butenediol was acting as a hydrogen source, then it would be possible alter the conditions to maximise the conversion and enantioselectivity.

3.8 Future work

There is scope to search for a catalyst that is able to perform better than the ruthenium catalysts investigated here. The concept of *cis*-1,4-butenediol and 1,4-butanediol as a hydrogen source has been shown to have great potential for the reduction of ketones.

Other ligands could be investigated, phosphine based ligands, or bulkier aminoethanol type ligands that showed good conversions but poor selectivity.

The scope of substrates examined here was rather limited and could be expanded upon, in particular aliphatic ketones. Imines could also be investigated, to synthesize enantiomerically pure amines from achiral starting materials would be desirable.

Results and Discussion III

Alcohols as a benign source of acylating agent

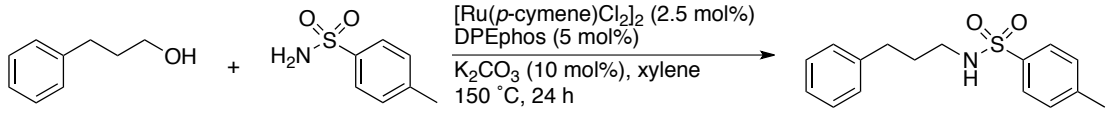
Alcohols as a benign source of acylating agent

Chapter 4: Results and Discussion III

4.1 Aims

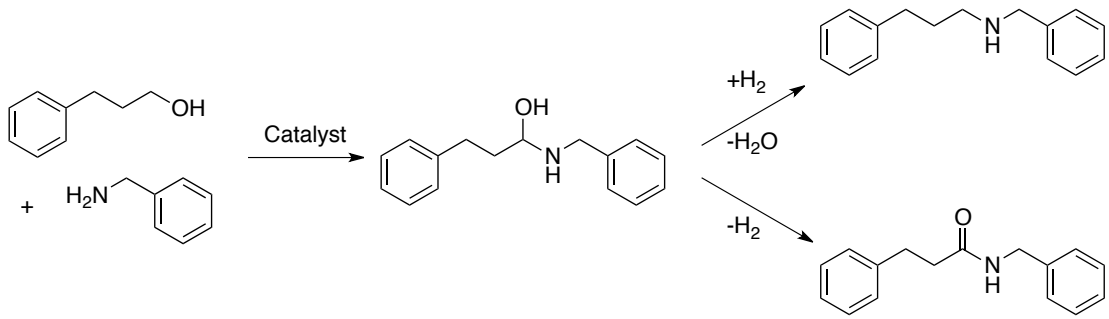
Aim of this work was to discover a suitable catalyst to couple alcohols and sulfonamides to form *N*-acylsulfonamides using transfer hydrogenation.

Previous work in the group considered the borrowing hydrogen transformation shown in Scheme 4.1.



Scheme 4.1

The *N*-alkylation of sulfonamides complemented the group's work on alkylation of amines using alcohols.[115] However, whilst investigating the alkylation of amines a side product of amide was noted. The possible pathways to this product are noted in Scheme 4.2.

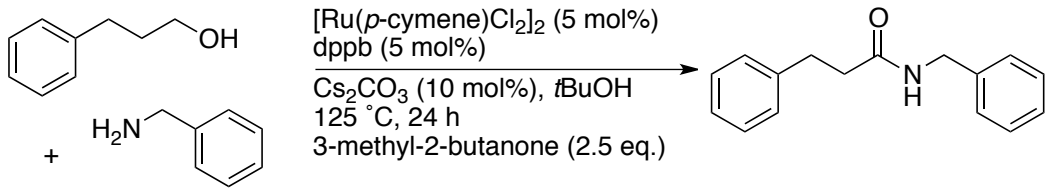


Scheme 4.2

Optimization of the amide pathway was conducted and was subsequently reported in the literature.[80-81, 116] Therefore it was considered that conditions could be found for the formation of *N*-acylsulfonamide from alcohol and sulfonamide coupling by stabilizing the hemiaminal intermediate sufficiently for oxidation to occur.

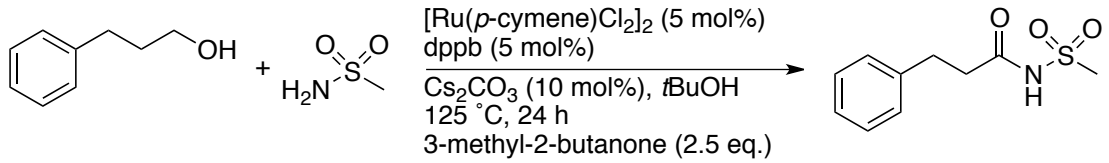
4.2 Initial work

Initially the conditions that had been seen to favour the pathway of the oxidation of the hemiaminal intermediate were focused on.



Scheme 4.3

The initial intention was to investigate whether the same conditions would result in acylation of sulfonamide with an alcohol starting material. Scheme 4.3 shows how the conditions were modified from alkylation to afford the oxidized amide product instead. The use of a hydrogen acceptor (3-methyl-2-butanone) in large excess is required.

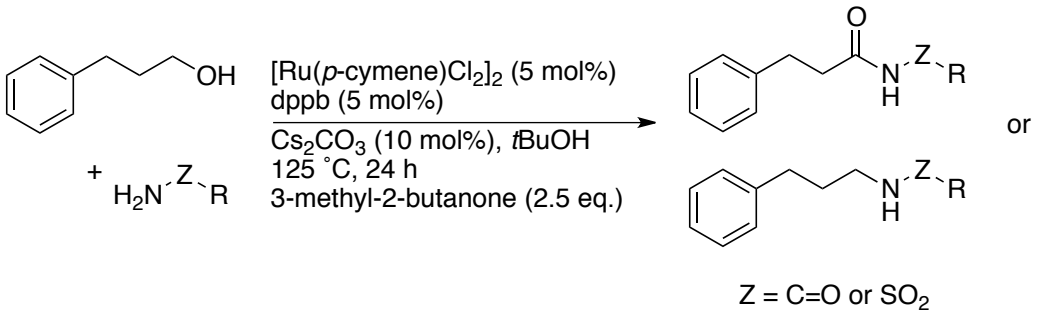


Scheme 4.4

Initially the reaction in Scheme 4.4 was investigated, which had identical conditions to Scheme 4.3. However, analysis of ^{1}H NMR spectra revealed that 3-phenylpropanol had *N*-alkylated methanesulfonamide to form compound **4.1** in 43% conversion rather than acylation.

When the sulfonamide substrate was changed to *p*-toluenesulfonamide a conversion of 79% into the *N*-alkylated product was observed. ^{1}H NMR peaks that corresponded to the *N*-acylated product were not observed. The conditions using primary amides and alcohols to determine if an imide could be formed were subsequently tested.

However, the only observed product was the corresponding secondary amide. The results are summarized in Table 4.1.



Z = C=O or SO_2

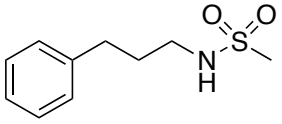
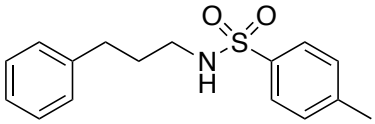
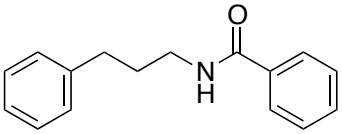
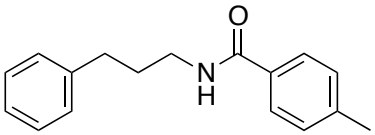
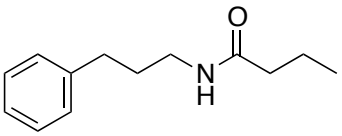
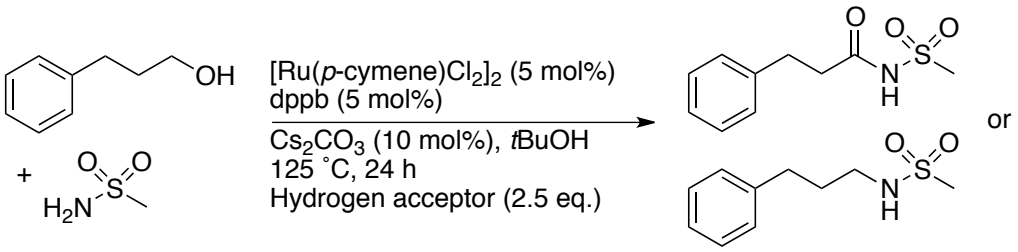
Entry	Compound	*N*-alkyl derivative[a]	% conversion[b]
1	**4.1**		43
2	**4.2**		79
3	**4.3**		29
4	**4.4**		6
5	**4.5**		19

Table 4.1. [a]Reactions were performed on a 3 mmol scale in 3 mL solvent. [b]Conversions determined by analysis of the ^{1}H NMR spectra.

It was necessary to test whether the hydrogen acceptor used had an effect on the pathway preference. It was hypothesized that if a very good hydrogen acceptor was used that the acylation pathway would be preferred.

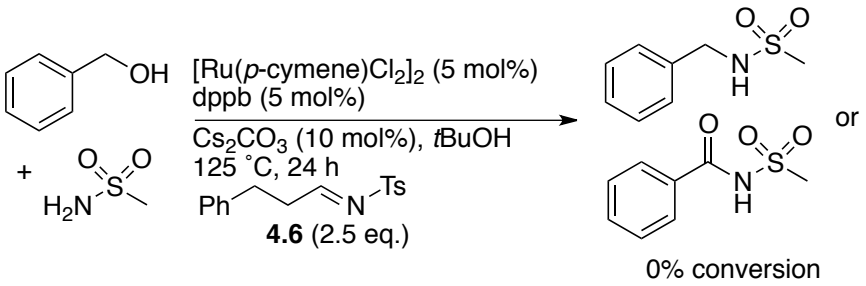


Entry	Hydrogen acceptor[a]	Alkylation (acylation) % conversion[b]
1	3-Methyl-2-butanone	43(0)
2	Benzophenone imine	4(0)
3	*N*-Benzylidine methylamine	29(0)
4	1,3-Cyclohexanedione	0(0)
5	Acetophenone	41(0)
6	Acetone	43(0)
7	Crotononitrile	49(0)

Table 4.2. [a]Reactions were performed on a 3 mmol scale in 3 mL solvent. [b]Conversions determined by analysis of the ^{1}H NMR spectra.

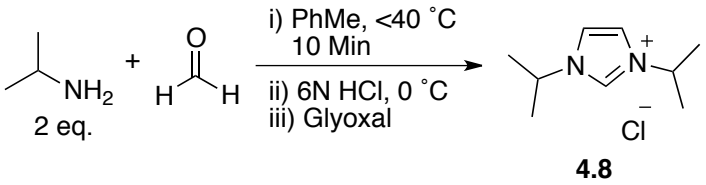
It was disappointing to observe that only alkylation occurred and that 3-methyl-2-butanone provided the best conversion for this small selection of hydrogen acceptors.

Subsequently sulfonimine **4.6** was synthesized to test if the imine intermediate that was suspected was being reduced to the alkylated product could be used in a sacrificial manner as the hydrogen acceptor. However, no acylation or alkylation was observed, only starting materials were observed, Scheme 4.5.



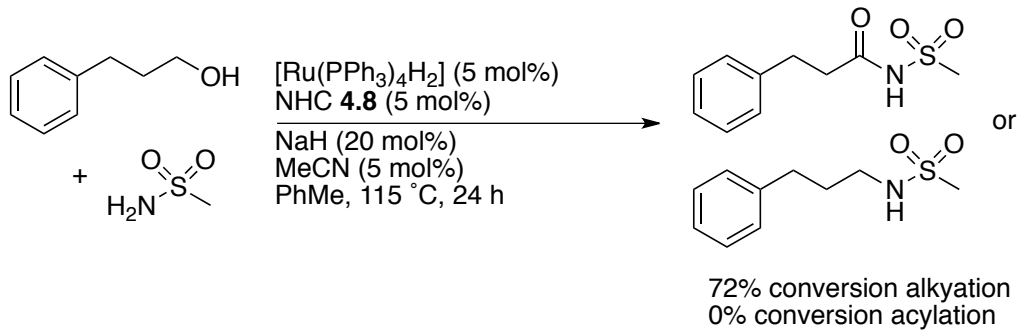
Scheme 4.5

Next other catalysts were considered that were known from the literature to act as transfer hydrogenation catalysts in the coupling of alcohols and amines to form amides.[82, 117] Initially the *N*-heterocyclic carbene (NHC) precursor **4.8** was synthesized using the method shown in Scheme 4.6.



Scheme 4.6[118]

The reaction in Scheme 4.7 was investigated based on previous work in the literature,[82] which had shown the formation of an amide from an alcohol and an amine. Under these conditions the reaction of methanesulfonamide and 3-phenyl-propanol showed 72% alkylation of the sulfonamide and no observable acylation.

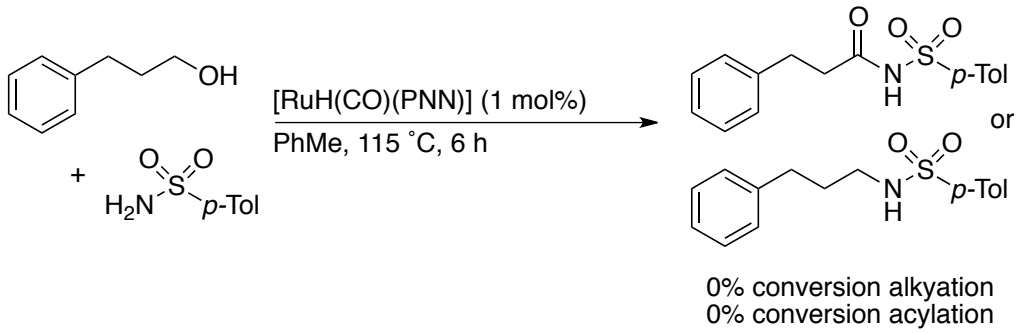


Scheme 4.7

It was hypothesized that the hemiaminal was still eliminating to give the sulfonimine, which was subsequently reduced to the *N*-alkylsulfonamide. The next step was to test these conditions on an amide substrate, however, no coupling was observed at all.

Then Milstein's catalyst was investigated. In 2007 Milstein had shown the first example of an amine and an alcohol coupling to form an amide using a ruthenium

catalyst.[80] With the intention of testing whether the same conditions could be applied to the acylation of a sulfonamide with an alcohol.



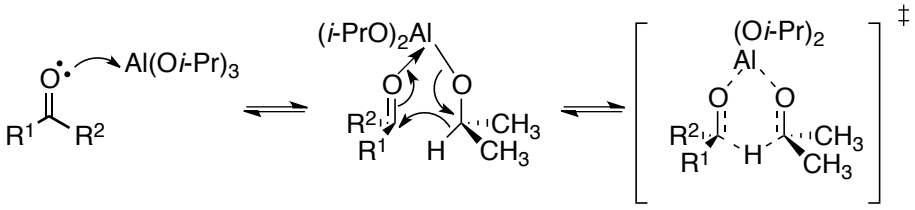
Scheme 4.8

The results shown in Scheme 4.8 show that no coupling between sulfonamide and alcohol was observed. The procedure was repeated for the coupling of an amide and an alcohol, however, no acylation or alkylation was observed.

At this stage it was decided that a different approach should be taken and to consider the other transfer hydrogenation mechanism, *Meerwein-Ponndorf-Verley*, to carry out the desired transformation.

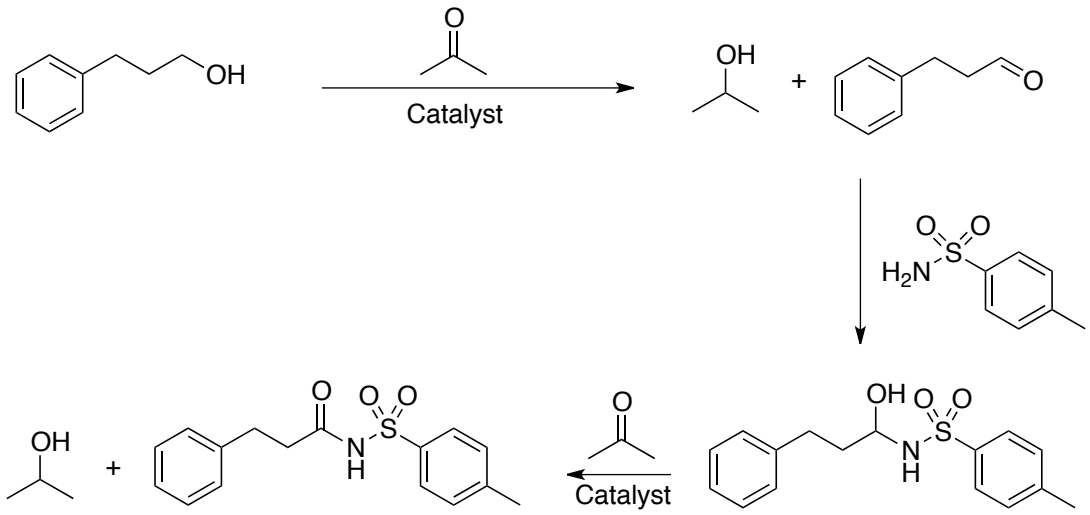
4.3 MPVO system

The *Meerwein-Ponndorf-Verley* (MPV) reduction mechanism is detailed in Scheme 4.9, it relies on a 6-membered transition state with a hydride transfer shift. The hydride shift is usually catalysed by an aluminium alkoxide catalyst.[58a, 62, 119] The *Oppenauer* oxidation mechanism is the reverse of MPV.



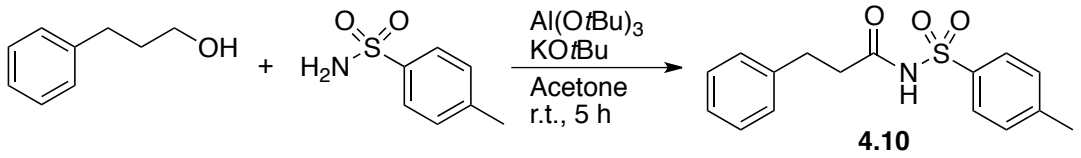
Scheme 4.9

Initially the potential of using standard MPVO conditions to acylate a sulfonamide with an alcohol was investigated. Scheme 4.10 shows the outline of the concept.



Scheme 4.10

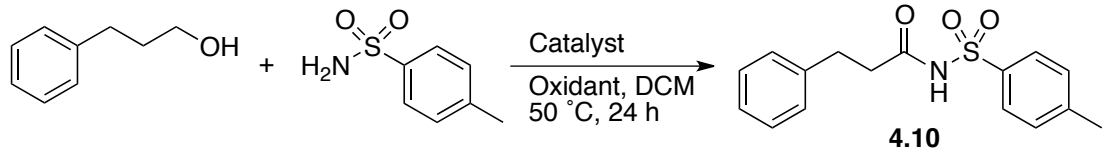
Initially aluminium alkoxide catalysts were considered and the effect of base on the performance of the MPVO catalyst was investigated.



Entry	Al(O*t*Bu)$_3$[a] (mol%)	KO*t*Bu (mol%)	*N*-Acylsulfonamide % conversion[b]
1	10	10	0
2	10	0	0
3	0	10	0
4	0	0	0
5	100	10	0
6	100	0	0

Table 4.3. [a]Reactions were performed on a 1 mmol scale in 3 mL solvent. [b]Conversions determined by analysis of the ^{1}H NMR spectra.

The results in Table 4.3 were disappointing. Therefore the oxidant was changed. IPA would have a greater affinity for the aluminium catalyst than 3-phenylpropanol, which might have been the reason for no reaction occurring. The temperature and reaction time were both increased to promote the reaction.



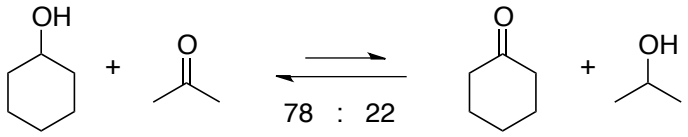
Entry	Oxidant[a] (1 eq.)	Catalyst (10 mol%)	*N*-acylsulfonamide % conversion[b]
1	Benzophenone	Al(O*t*Bu)$_3$	0
2	Cyclohexanone	Al(O*t*Bu)$_3$	0
3	Benzophenone	Al(O*i*Pr)$_3$	0
4	Benzophenone	AlMe$_2$Cl	0
5	Cyclohexanone	AlMe$_2$Cl	0
6	Benzophenone	AlMe$_2$Cl[c]	0
7	Benzophenone	AlMe$_3$[d]	0

Table 4.4. [a]Reactions were performed on a 1 mmol scale in 2 mL solvent. [b]Conversions determined by analysis of the ^{1}H NMR spectra. [c]Reaction performed at 110 ˚C with 1 mmol KO*t*Bu. [d]Reaction performed at 110 ˚C with 1 mmol K_2CO_3.

Table 4.4 shows the results when the oxidant, catalyst and conditions were varied. No coupling at all was observed and merely observed starting materials.

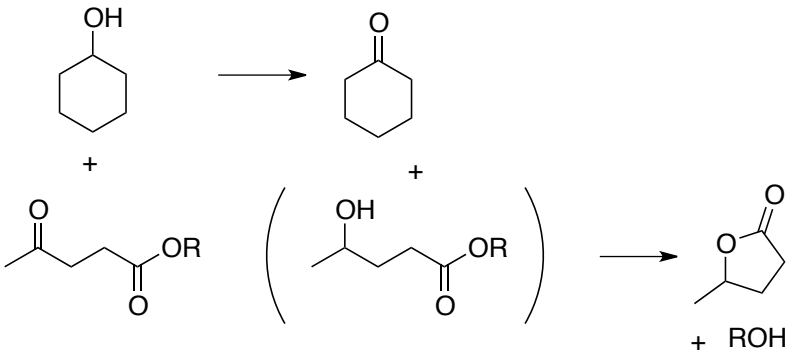
4.4 Methyl levulinate

Previous work in the group had shown methyl levulinate to be an excellent hydrogen acceptor.[120] Scheme 4.11 shows the equilibrium problem that occurs with transfer hydrogenation reactions of this type.



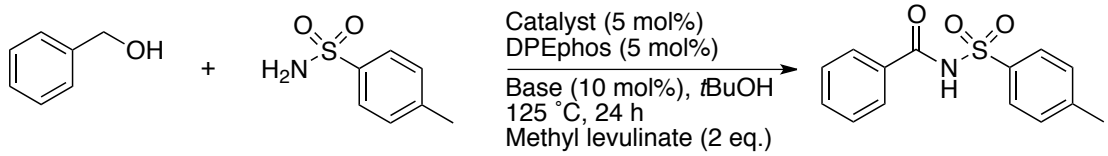
Scheme 4.11

The equilibrium lies to the left of the equation. This is a problem if one desires the oxidation of cyclohexanol to proceed. Methyl levulinate performs as an excellent hydrogen acceptor because lactonisation can occur after the initial reduction and the molecule acts as an intramolecular trap, shown in Scheme 4.12.



Scheme 4.12

Methyl levulinate was tested with a variety of catalysts, the results are shown in Table 4.5.

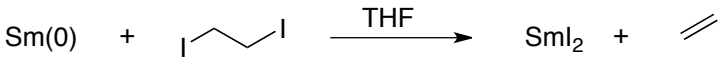


Entry	Catalyst[a]	Base	% conversion[b]
1	$Ru(PPh_3)_3(CO)H_2$	Cs_2CO_3	0
2	$Ru(PPh_3)_3(CO)H_2$	KO*t*Bu	0
3	$[Ru(p\text{-cymene})Cl_2]_2$	Cs_2CO_3	0
4	$[Ru(p\text{-cymene})Cl_2]_2$	KO*t*Bu	0
5	$Al(OiPr)_3$	Cs_2CO_3	0
6	$Al(OtBu)_3$	Cs_2CO_3	0
7	$AlMe_3$	Cs_2CO_3	0
8	$Al(OiPr)_3$	KO*t*Bu	0
9	$Al(OtBu)_3$	KO*t*Bu	0
10	$AlMe_3$	KO*t*Bu	0

Table 4.5. [a]Reactions were performed on a 1 mmol scale in 2 mL solvent. [b]Conversions determined by analysis of the ^{1}H NMR spectra.

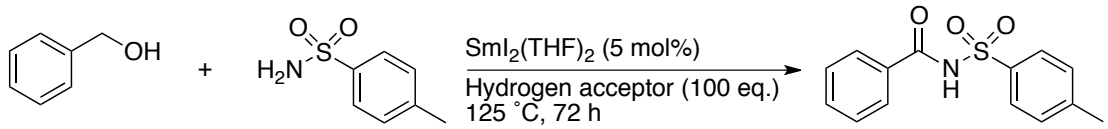
It was disappointing to discover that methyl levulinate did not show any coupling between the sulfonamide and alcohol.

A solution of SmI_2 in THF was then synthesized using a literature procedure[121] and tested the SmI_2 catalyst.



Scheme 4.13

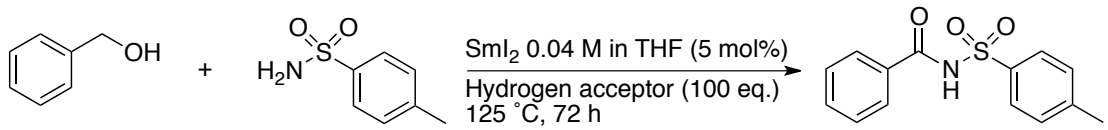
Previous work in the literature had shown that SmI_2 in THF and $SmI_2(THF)_2$ can be effective MPVO catalysts using IPA as the hydrogen source.[122] Therefore it seemed prudent to test whether these catalysts showed any activity in the acylation of sulfonamides in an MPVO system. Table 4.6 summarizes the results for $SmI_2(THF)_2$.



Entry	Hydrogen acceptor[a]	Alkyl, acyl or imine product % conversion[b]
1	Cyclohexanone	0, 0, 0
2	4-Nitroacetophenone	0, 0, 0
3	Acrylonitrile	0, 0, 18
4	Methyl levulinate[c]	0, 0, 0

Table 4.6. [a]Reactions were performed on a 1 mmol scale. [b]Conversions determined by analysis of the ^{1}H NMR spectra. [c]Reaction performed with 4 mmol methyl levulinate.

The disappointing results in Table 4.6 show that only acrylonitrile showed any activity at all and that only a small conversion into the sulfonimine product was observed. Table 4.7 shows the results for SmI_2 in THF.

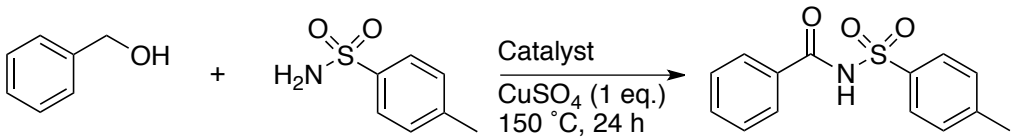


Entry	Hydrogen acceptor[a]	Alkyl, acyl or imine product % conversion[b]
1	Cyclohexanone	0, 0, 0
2	4-Nitroacetophenone	0, 0, 0
3	Acrylonitrile	0, 0, 8
4	Methyl levulinate[c]	0, 0, 0
5	Acetone	0, 0, 0
6	Crotononitrile	0, 0, 0

Table 4.7. [a]Reactions were performed on a 1 mmol scale. [b]Conversions determined by analysis of the ^{1}H NMR spectra. [c]Reaction performed with 4 mmol methyl levulinate.

It was disappointing again that only acrylonitrile showed any activity at all. It was apparent that benzyl alcohol could be oxidized to benzaldehyde but that SmI_2 could not catalyse the coupling of benzaldehyde and *p*-toluenesulfonamide.

The final attempt to try to solve this issue involved using $CuSO_4$ as the oxidant and testing whether another catalyst could carry out the coupling reaction between the aldehyde generated and the sulfonamide. Initially a rhodium catalyst was used that was known in the literature to couple aldehydes and sulfonamides in the presence of an oxidant.[53] A copper(I) catalyst was also considered as a cheaper alternative to rhodium.



Entry	Catalyst[a]	Alkyl, acyl or imine product % conversion[b]
1	No catalyst	46, 0, <5
2	$Rh_2(OAc)_4$ (2 mol%)	<5, 0, 67
3	Cu(OTf).MeCN (10 mol%)	67, 0, 20
4	$FeCl_2$/pyridine[c]	0, 0, <5
5	Ru(*p*-cymene)Cl_2[d]	0, 0, 8

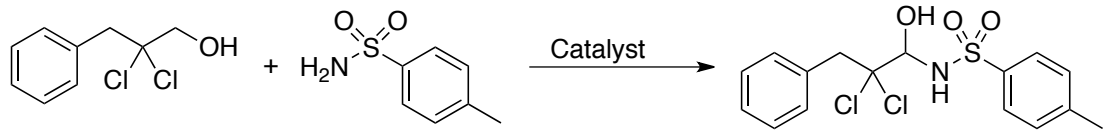
Table 4.8. [a]Reactions were performed on a 1 mmol scale using 4 mmol benzyl alcohol. [b]Conversions determined by analysis of the ^{1}H NMR spectra. [c]Reaction performed with 0.1 mmol $FeCl_2$ and 0.4 mmol pyridine. [d]Reaction performed with 1.1 mmol benzyl alcohol.

The results shown in Table 4.8 were disappointing. Only alkylation and sulfonimine formation could be achieved. Several side products were observed in these reactions, the formation of the Tishchenko by-product, benzyl benzoate was observed and also the formation of benzaldehyde. This indicates that the oxidation of benzyl alcohol to benzaldehyde occurs but that the addition of sulfonamide leads only to formation of the hemiaminal that eliminates to give the sulfonimine, which is subsequently hydrogenated under certain conditions.

4.5 Conclusion

The principle of *N*-acylation of sulfonamides using benign alcohol as the acylating agent is a good one. The analogous reaction can be performed on amides as shown in the literature and by previous work in the group. However, using the catalytic systems presented here, the sulfonamide reaction could not be achieved. All attempts either returned starting materials or resulted in sulfonimine formation and subsequent reduction to the *N*-alkyl product. The results were very disappointing. It is still possible that there is a catalyst or catalyst system that will perform this reaction. The key step is to stabilize the hemiaminal and prevent elimination to the sulfonimine.

4.6 Future work



Scheme 4.13

The final experiments that were conducted on this project involved attempting to synthesize 2,2-dichloro-3-phenyl-propanol from commercially available 3-phenyl-propanol with the aim to test whether the presence of α-chlorines adjacent to the hemiaminal would stabilize it enough to allow oxidation to occur prior to the elimination reaction that occurs when the α atoms are hydrogen. However, time constraints meant that it has not yet been tested whether stabilizing the hemiaminal in this manner will in fact lead to preventing elimination. This would therefore be suitable for future work, in conjunction with the ongoing search for a catalyst that can perform this transformation.

Experimental

Chapter 5: Experimental

5.1 General Experimental Methods

All reactions requiring an anhydrous, inert atmosphere were carried out under an argon atmosphere using evacuated carousel or ampules. Unless preparative details are provided, all reagents were purchased from commercial suppliers Acros Organics, Aldrich, Alfa Aesar, Fluka, Lancaster, Maybridge, Strem or TCI UK and used without further purification. Thin layer chromatography was carried out on aluminium or plastic backed silica plates, purchased from Aldrich. The plates were visualised under UV (254 nm) light, followed by staining with phosphomolybdic acid dip or potassium permanganate and gentle heating. During compound separations, column chromatography was carried out using 60 micron dry silica purchased from Aldrich. Organic layers were routinely dried with anhydrous $MgSO_4$ and concentrated using a Büchi rotary evaporator.

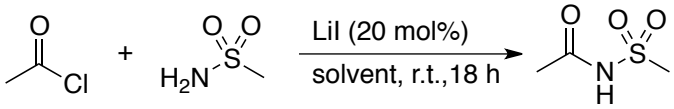
^{1}H NMR / ^{13}C NMR spectra were run in deuterated (≥99.5%) solvents purchased from Fluorochem unless stated otherwise, on a Bruker Avance 300 (300 MHz ^{1}H, 75 MHz ^{13}C) or Bruker Avance 250 (250 MHz ^{1}H, 62.5 MHz ^{13}C). Any chemical shifts (δ) are reported as parts per million (ppm) with reference to tetramethylsilane (TMS) (δH = 0.00 ppm) unless otherwise stated. The coupling constants (*J*) are reported in Hz and signal multiplicities are reported as singlet (s), doublet (d), triplet (t), quartet (q), quintet (qu), doublet of doublets (dd), doublet of triplets (dt), triplet of triplets (tt), multiplet (m), or broad singlet (br. s).

For mass spectrometry data acquisition a micrOTOF electrospray time-of-flight (ESI-TOF) mass spectrometer (Bruker Daltonik, GmbH, Bremen, Germany) was used; this was coupled to an Agilent 1200 LC system (Agilent Technologies, Waldbronn, Germany). The LC system was used as an auto sampler only. 10 µL of sample was injected into a 30:70 flow of water:acetonitrile at 0.3 mL/min to the mass spectrometer. For each acquisition 10 µL of a calibrant of 5 mM sodium formate was injected after the sample. The observed mass and isotope pattern matched the corresponding theoretical values as calculated from the expected elemental formula.

Infrared spectra were recorded on a Perkin Elmer Spectrum 100 FT-IR spectrometer, using a Universal ATR accessory for sampling, with relevant absorbance quoted as ν in cm^{-1}. Optical rotations were measured on an AA-10 Automatic Polarimeter. HPLC traces were measured using a Perkin Elmer 200 Series HPLC system. Enantiomeric excess measurements were carried out using a Chiracel column as specified for each compound, eluting with HPLC grade hexane and isopropyl alcohol. All other HLPC experiments were carried out using a Phenomenex Prodigy 5 μm column and an acetonitrile (0.05% TFA): water (0.05% TFA) gradient elution system. Melting points were determined using Stuart SMP10 melting point equipment using closed end glass capillary tubes and are uncorrected. Specific rotations were determined on an Optical Activity LTD: AA-10 automatic polarimeter.

5.2 Chapter 2 Experimental Methods

Representative Procedure I (Chapter 2, Section 2.2)



To oven dried Radleys carousel tubes lithium iodide and methanesulfonamide were added, the appropriate anhydrous solvent dissolved the reagents, acid chloride was added to the solution using a micropipette. The tube was then sealed and the reaction mixture was immediately heated to the appropriate temperature and stirred for the appropriate amount of time. The resulting reaction mixture was then washed with DCM and sodium thiosulfate solution. The organic components were then dried and concentrated *in vacuo*. The resulting products were analysed by their ^{1}H NMR spectra.

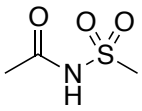
Solvent Screen

(Table 2.1 – Chapter 2, Section 2.2.1)

Following representative procedure I, the appropriate anhydrous solvent (2 mL) was used according to Table 2.1. Lithium iodide (54 mg, 0.4 mmol, 20 mol%), methanesulfonamide (190 mg, 2 mmol) and acetyl chloride (142 μL, 2 mmol) were used, the reaction was performed at room temperature for 18 hours. The ^{1}H NMR of

the crude reaction mixture showed % conversion by comparison of the peaks at 3.25 (3H, s, CH_3, **2.1**) and 3.15 (3H, s, CH_2, methanesulfonamide). ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 8.69 (1H, br.s, NH), 3.25 (3H, s, CH_3), 2.09 (3H, s, CH_3).

2.1 - *N*-Methanesulfonylacetamide[98]



Following representative procedure I, the title compound was recovered and the ^{1}H NMR of the crude product analysed. ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 8.69 (1H, br.s, NH), 3.25 (3H, s, CH_3), 2.09 (3H, s, CH_3).

Variation of lithium iodide loading

(Table 2.2, Chapter 2, Section 2.2.1)

Following representative procedure I, the appropriate amount of lithium iodide was used according to Table 2.2. Methanesulfonamide (476 mg, 5 mmol), acetyl chloride (356 μL, 5 mmol) and anhydrous MeCN (5 mL) were used the reaction was performed at room temperature for 18 hours. The ^{1}H NMR of the crude reaction mixture showed % conversion by comparison of the peaks at 3.25 (3H, s, CH_3, **2.1**) and 3.15 (3H, s, CH_2, methanesulfonamide). ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 8.69 (1H, br.s, NH), 3.25 (3H, s, CH_3), 2.09 (3H, s, CH_3).

Variation of acid chloride

(Table 2.3, Chapter 2, Section 2.2.1)

Following representative procedure I, the appropriate acid chloride (1 mmol) was used according to Table 2.3. Lithium iodide (134 mg, 1 mmol), methanesulfonamide (95 mg, 1 mmol) and anhydrous MeCN (1 mL) were used the reaction was performed at room temperature for 18 hours. Where appropriate the reaction mixture was heated to 40 ˚C and after the 18 hour reaction time, cooled to room temperature before extraction. The ^{1}H NMR: ($CDCl_3$, 300 MHz) of the crude reaction mixture showed % conversion by comparison of the peaks at 3.48 (3H, s, CH_3, **2.2**), 3.25 (3H, s, CH_3, **2.1**) and 3.15 (3H, s, CH_2, methanesulfonamide).

Competition experiment

(Scheme 2.5, Chapter 2, Section 2.2.1)

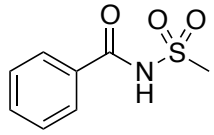
Following representative procedure I, benzoyl chloride (116 μL, 1 mmol), acetyl chloride (72 μL, 1 mmol), lithium iodide (134 mg, 1 mmol), methanesulfonamide (95 mg, 1 mmol) and anhydrous MeCN (1 mL) were used, the reaction was performed at room temperature for 18 hours. The ^{1}H NMR: ($CDCl_3$, 300 MHz) of the crude reaction mixture showed % conversion by comparison of the peaks at 3.48 (3H, s, CH_3, **2.2**), 3.25 (3H, s, CH_3, **2.1**) and 3.15 (3H, s, CH_2, methanesulfonamide).

Changing the acid chloride with variation of lithium iodide loading

(Table 2.4, Chapter 2, Section 2.2.1)

Following representative procedure I, the appropriate amount of lithium iodide was used according to Table 2.4. Methanesulfonamide (190 mg, 2 mmol), benzoyl chloride (232 μL, 2 mmol) and anhydrous MeCN (2 mL) were used, the reaction was performed at 82 ˚C for 20 hours. The ^{1}H NMR: ($CDCl_3$, 250 MHz) of the crude reaction mixture showed % conversion by comparison of the peaks at 3.48 (3H, s, CH_3, **2.2**) and 3.15 (3H, s, CH_2, methanesulfonamide).

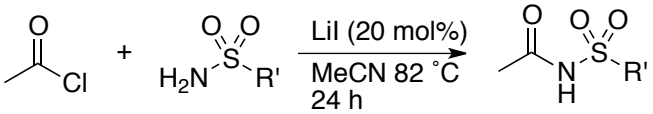
2.2 - *N*-(Methylsulfonyl)benzamide[99]



Following representative procedure I, the title compound was recovered and the ^{1}H NMR of the crude product analysed. ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 8.93 (1H, br.s, NH), 7.90 (2H, d, *J* = 7.7 Hz, Ar), 7.63 – 7.47 (3H, m, Ar), 3.48 (3H, s, CH_3).

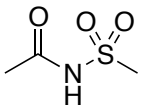
Representative Procedure II

(Table 2.5, Chapter 2, Section 2.2.1)



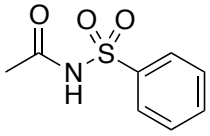
To oven dried Radleys carousel tubes lithium iodide (134 mg, 1 mmol, 20 mol%) and sulfonamide were added, anhydrous MeCN (2 mL) dissolved the reagents and acid chloride was added to the solution using a micropipette. The tube was then sealed and the reaction mixture was heated to 82 ˚C and stirred for 24 hours. The resulting reaction mixture was then washed with DCM and sodium thiosulfate solution. The organic components were then dried and concentrated *in vacuo*. The crude product was then purified using column chromatography using EtOAc/hexane 1:2, unless otherwise stated. The resulting products were analysed by their ^{1}H and ^{13}C NMR spectra and mass spectrometry data.

2.1 - *N*-Methanesulfonylacetamide[98]



Following representative procedure II, methanesulfonamide (476 mg, 5 mmol) was used as the sulfonamide species and acetyl chloride (427 µL, 6 mmol) was used as the acid chloride species. The title compound was recovered as a yellow solid (0.130 g, 19%). ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 8.69 (1H, br.s, NH), 3.25 (3H, s, CH_3), 2.09 (3H, s, CH_3). ^{13}C NMR: ($CDCl_3$, 75.5 MHz) δ 171.8, 43.4, 23.5. ESI-MS of [$C_3H_7NO_3S$]; theoretical m/z of $[M+Na]^+$ = 160.0044, measured m/z of $[M+Na]^+$ = 160.0032.

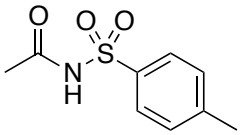
2.3 *N*-Benzenesulfonylacetamide[98]



Following representative procedure II, benzenesulfonamide (786 mg, 5 mmol) was used as the sulfonamide species and acetyl chloride (427 µL, 6 mmol) was used as the acid chloride species. The title compound was recovered as a yellow solid (0.839

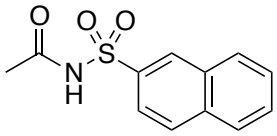
g, 84%). ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 8.67 (1H, br.s, NH), 8.10 (2H, d, *J* = 8.1 Hz, Ar), 7.77 – 7.52 (3H, m, Ar), 2.11 (3H, s, CH_3). ^{13}C NMR: ($CDCl_3$, 75.5 MHz) δ 168.7, 138.5, 134.1, 129.1, 128.2, 23.5. ESI-MS of [$C_8H_9NO_3S$]; theoretical m/z of $[M+H]^+$ = 200.0381, measured m/z of $[M+H]^+$ = 200.0378.

2.4 - *N*-Tosylacetamide[98]



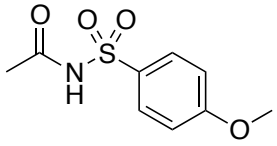
Following representative procedure II, *p*-toluenesulfonamide (856 mg, 5 mmol) was used as the sulfonamide species and acetyl chloride (427 µL, 6 mmol) was used as the acid chloride species. The title compound was recovered as a yellow solid (0.999 g, 94%). ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 8.73 (1H, br.s, NH), 7.81 (2H, d, *J* = 8.2 Hz, Ar), 7.22 (2H, d, *J* = 8.2 Hz, Ar), 2.32 (3H, s, CH_3), 1.94 (3H, s, CH_3). ^{13}C NMR: ($CDCl_3$, 75.5 MHz) δ 168.2, 145.3, 135.5, 129.7, 128.3, 23.5, 21.7. ESI-MS of [$C_9H_{11}NO_3S$]; theoretical m/z of $[M-H]^-$ = 212.0381, measured m/z of $[M-H]^-$ = 212.0384.

2.5 - *N*-(Naphthalen-2-ylsulfonyl)acetamide[123]



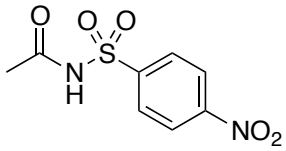
Following representative procedure II, naphthalene sulfonamide (1.036 g, 5 mmol) was used as the sulfonamide species and acetyl chloride (427 µL, 6 mmol) was used as the acid chloride species. The title compound was recovered as a yellow solid (1.016 g, 90%). ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 8.94 (1H, br.s, NH), 8.68 (1H, s, Ar), 8.06 – 7.87 (2H, m, Ar), 7.74 – 7.59 (4H, m, Ar), 2.09 (3H, s, CH_3). ^{13}C NMR: ($CDCl_3$, 75.5 MHz) δ 168.3, 135.5, 135.2, 131.9, 130.5, 129.6, 129.5, 129.4, 128.0, 127.8, 122.6, 23.6. ESI-MS of [$C_{12}H_{11}NO_3S$]; theoretical m/z of $[M-H]^-$ = 248.0381, measured m/z of $[M-H]^-$ = 248.0383.

2.6 - *N*-(4-Methoxybenzenesulfonyl)acetamide[98]



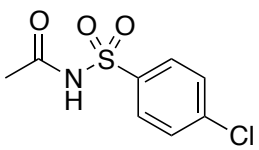
Following representative procedure II, 4-methoxybenzene sulfonamide (936 mg, 5 mmol) was used as the sulfonamide species and acetyl chloride (427 µL, 6 mmol) was used as the acid chloride species. The title compound was recovered as a yellow solid (1.027 g, 90%). ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 8.81 (1H, br.s, NH), 7.92 (2H, d, *J* = 9.1 Hz, Ar), 6.93 (2H, d, *J* = 9.1 Hz, Ar), 3.81 (3H, s, CH_3), 1.99 (3H, s, CH_3). ^{13}C NMR: ($CDCl_3$, 75.5 MHz) δ 168.3, 164.0, 130.7, 129.8, 114.2, 55.8, 23.5. ESI-MS of [$C_9H_{11}NO_4S$]; theoretical m/z of $[M-H]^-$ = 228.0331, measured m/z of $[M-H]^-$ = 228.0330.

2.7 - *N*-(4-Nitrobenzene)sulfonylacetamide[98]



Following representative procedure II, 4-nitrobenzene sulfonamide (1.011 g, 5 mmol) was used as the sulfonamide species and acetyl chloride (427 µL, 6 mmol) was used as the acid chloride species. The title compound was recrystallised from hot ethanol and distilled water, the product was isolated by filtration as a pale yellow solid (1.059 g, 87%). ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 8.71 (1H, br.s, NH), 8.42 (2H, d, *J* = 8.8 Hz, Ar), 8.30 (2H, d, *J* = 8.8 Hz, Ar), 2.11 (3H, s, CH_3). ^{13}C NMR: ($CDCl_3$, 75.5 MHz) δ 169.5, 150.6, 144.8, 129.6, 124.8, 23.6. ESI-MS of [$C_8H_8N_2O_5S$]; theoretical m/z of $[M-H]^-$ = 243.0076, measured m/z of $[M-H]^-$ = 243.0092.

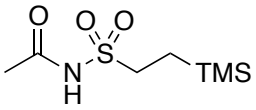
2.8 - *N*-(4-Chlorobenzene)sulfonylacetamide[123]



Following representative procedure II, 4-chlorobenzene sulfonamide (958 mg, 5 mmol) was used as the sulfonamide species and acetyl chloride (427 µL, 6 mmol)

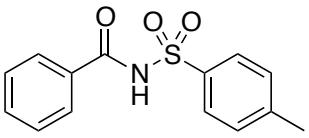
was used as the acid chloride species. The title compound was recrystallised from hot ethanol and distilled water, the product was isolated by filtration as a pale yellow solid (0.972 g, 83%). ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 8.09 (1H, br.s, NH), 7.94 (2H, d, *J* = 8.8 Hz, Ar), 7.46 (2H, d, *J* = 8.8 Hz, Ar), 2.01 (3H, s, CH_3). ^{13}C NMR: ($CDCl_3$, 75.5 MHz) δ 169.3, 139.0, 138.5, 129.9, 129.6, 23.6. ESI-MS of [$C_8H_8ClNO_3S$]; theoretical m/z of $[M-H]^-$ = 231.9835, measured m/z of $[M-H]^-$ = 231.9837.

2.9 - *N*-Trimethylsilylethyl sulfonylacetamide



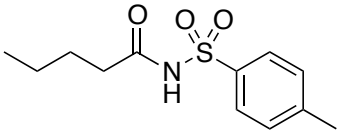
Following representative procedure II, trimethylsilylethyl sulfonamide (663 mg, 3.65 mmol) was used as the sulfonamide species and acetyl chloride (427 µL, 6 mmol) was used as the acid chloride species. The title compound was isolated as a yellow solid (0.734 g, 90%), mp 79-81 ˚C. ^{1}H NMR: ($CDCl_3$, 250 MHz) δ 8.56 (1H, br.s, NH), 3.38 – 3.22 (2H, m, CH_2), 2.09 (3H, s, CH_3), 1.03 – 0.88 (2H, m, CH_2), 0.0 (9H, s, $SiCH_3$). ^{13}C NMR: ($CDCl_3$, 75.5 MHz) δ 171.2, 52.2, 25.6, 11.9, 0.0. IR (film, cm^{-1}): ν_{max} = 1699 (C=O). ESI-MS of [$C_7H_{17}NO_3SSi$]; theoretical m/z of $[M-H]^-$ = 222.0620, measured m/z of $[M-H]^-$ = 222.0616. Requires C 37.52%; H 7.66%; N 6.34%, found: C 37.55%; H 7.62%; N 6.38 %.

2.10 - *N*-Tosylbenzamide[123]



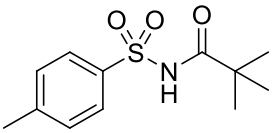
Following representative procedure II, *p*-toluenesulfonamide (856 mg, 5 mmol) was used as the sulfonamide species and benzoyl chloride (697 µL, 6 mmol) was used as the acid chloride species. The ^{1}H NMR of the crude reaction mixture showed 13% conversion. ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 9.36 (1H, br.s, NH), 7.97 (2H, d, *J* = 8.0 Hz, Ar), 7.75 (2H, d, *J* = 8.4 Hz, Ar), 7.56-7.40 (1H, m, Ar), 7.34 (2H, t, *J* = 8.0 Hz, Ar), 7.27 (2H, d, *J* = 8.4 Hz, Ar), 2.36 (3H, s, CH_3). ^{13}C NMR: ($CDCl_3$, 75.5 MHz) δ 164.4, 145.3, 135.5, 133.5, 131.1, 129.7, 128.7, 127.9, 21.75.

2.11 - *N*-Tosylpentanamide[48]



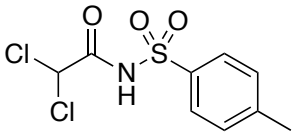
Following representative procedure II, *p*-toluenesulfonamide (856 mg, 5 mmol) was used as the sulfonamide species and valeroyl chloride (712 µL, 6 mmol) was used as the acid chloride species. The ^{1}H NMR of the crude reaction mixture showed 98% conversion. ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 9.13 (1H, br.s, NH), 7.94 (2H, d, *J* = 8.2 Hz, Ar), 7.34 (2H, d, *J* = 8.2 Hz, Ar), 2.43 (3H, s, CH_3), 2.31-2.20 (2H, m, CH_2), 1.52 (2H, m, CH_2), 1.24 (2H, m, CH_2), 0.82 (3H, t, *J* = 7.3 Hz, CH_3). ^{13}C NMR: ($CDCl_3$, 75.5 MHz) δ 171.5, 145.2, 135.6, 129.7, 128.3, 36.0, 26.3, 22.0, 21.7, 13.7.

2.12 - *N*-Tosylpivalamide[123]



Following representative procedure II, *p*-toluenesulfonamide (856 mg, 5 mmol) was used as the sulfonamide species and trimethylacetyl chloride (739 µL, 6 mmol) was used as the acid chloride species. The ^{1}H NMR of the crude reaction mixture showed 86% conversion. ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 8.74 (1H, br.s, NH), 7.88 (2H, d, *J* = 8.2 Hz, Ar), 7.27 (2H, d, *J* = 8.2 Hz, Ar), 2.37 (3H, s, CH_3), 1.07 (9H, s, CH_3). ^{13}C NMR: ($CDCl_3$, 75.5 MHz) δ 176.2, 145.0, 135.5, 129.6, 128.4, 40.0, 26.7, 21.7.

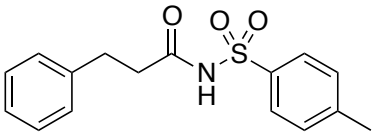
2.13 - *N*-Tosyldichloroacetamide[124]



Following representative procedure II, *p*-toluenesulfonamide (856 mg, 5 mmol) was used as the sulfonamide species and dichloroacetyl chloride (577 µL, 6 mmol) was used as the acid chloride species. The ^{1}H NMR of the crude reaction mixture showed 61% conversion. ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 9.03 (1H, br.s, NH), 7.90 (2H, d, *J* = 8.3

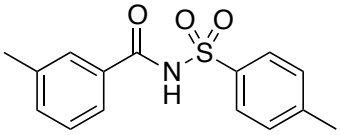
Hz, Ar), 7.31 (2H, d, *J* = 8.3 Hz, Ar), 5.78 (1H, s, CH), 2.39 (3H, s, CH_3). ^{13}C NMR: ($CDCl_3$, 75.5 MHz) δ 160.9, 146.1, 134.1, 129.9, 128.7, 65.6, 21.8.

2.14 - 3-Phenyl-*N*-tosylpropanamide[125]



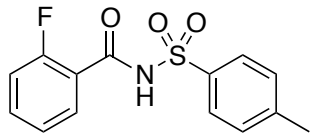
Following representative procedure II, *p*-toluenesulfonamide (856 mg, 5 mmol) was used as the sulfonamide species and hydrocinnamoyl chloride (892 µL, 6 mmol) was used as the acid chloride species. The ^1H NMR of the crude reaction mixture showed 97% conversion. ^1H NMR: ($CDCl_3$, 300 MHz) δ 9.03 (1H, br.s, NH), 7.89 (2H, d, *J* = 8.3 Hz, Ar), 7.31 (2H, d, *J* = 8.3 Hz, Ar), 7.25-7.13 (3H, m, Ar), 7.06 (2H, m, Ar), 2.86 (2H, t, *J* = 7.7 Hz, CH_2), 2.56 (2H, t, *J* = 7.7 Hz, CH_2), 2.45 (3H, s, CH_3). ^{13}C NMR: ($CDCl_3$, 75.5 MHz) δ 170.5, 145.2, 139.7, 135.4, 129.7, 128.6, 128.4, 128.3, 126.4, 37.9, 30.3, 21.8.

2.15 - 3-Methyl-*N*-tosylbenzamide[126]



Following representative procedure II, *p*-toluenesulfonamide (856 mg, 5 mmol) was used as the sulfonamide species and *m*-toluoyl chloride (791 µL, 6 mmol) was used as the acid chloride species. The ^1H NMR of the crude reaction mixture showed 22% conversion. ^1H NMR: ($CDCl_3$, 300 MHz) δ 8.73 (1H, br.s, NH), 7.97 (2H, m, Ar), 7.85 (2H, d, *J* = 7.9 Hz, Ar), 7.65-7.47 (2H, m, Ar), 7.41 (2H, d, *J* = 7.9, Ar), 2.45 (3H, s, CH_3), 2.41 (3H, s, CH_3). ^{13}C NMR: ($CDCl_3$, 75.5 MHz) δ 166.3, 145.2, 138.0, 135.5, 132.1, 131.8, 131.7, 129.7, 128.5, 127.3, 126.0, 21.8, 20.1.

2.16 - 2-Fluoro -*N*-tosylbenzamide[125]

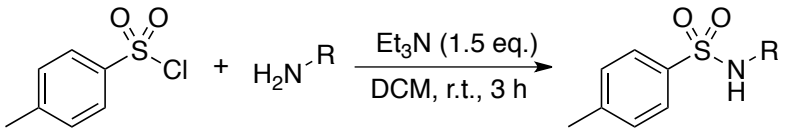


Following representative procedure II, *p*-toluenesulfonamide (856 mg, 5 mmol) was used as the sulfonamide species and 2-fluorobenzoyl chloride (717 µL, 6 mmol) was used as the acid chloride species. The ^{1}H NMR of the crude reaction mixture showed <5% conversion. ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 9.07 (1H, br.s, NH), 8.07 - 7.64 (3H, m, Ar), 7.52 - 7.35 (1H, m, Ar), 7.30-6.95 (4H, m, Ar), 2.32 (3H, s, CH_3).

Acylation of Secondary Sulfonamide (Chapter 2, Section 2.2)

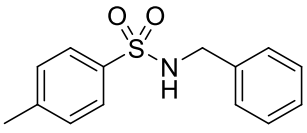
Representative Procedure III

(Scheme 2.6, Chapter 2, Section 2.2.2)



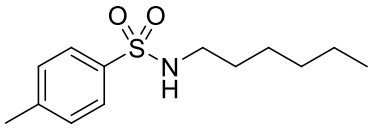
To oven dried Radleys carousel tubes *p*-toluenesulfonyl chloride (3.813 g, 20 mmol) and triethylamine (4.2 mL, 30 mmol, 1.5 eq.) were added, anhydrous DCM (30 mL) dissolved the reagents, amine was added to the solution using a syringe. The tube was then sealed and the reaction mixture was stirred at room temperature for 3 hours. The product crashed out of solution and could then be filtered off and dried using a Buchner funnel. The products were then recrystallized from layered hexane on a DCM solution. The resulting products were analysed by their ^{1}H NMR spectra.

2.17 - *N*-Benzyl-4-methylbenzene sulfonamide[127]



Following representative procedure III, benzylamine (2.2 mL, 20 mmol) was used as the amine species. The title compound was recovered as a white solid (5.122 g, 98%). ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 7.79 (2H, d, *J* = 8.3 Hz, Ar), 7.38 – 7.19 (7H, m, Ar), 4.83 (1H, t, *J* = 6.1 Hz, NH), 4.14 (2H, d, *J* = 6.1 Hz, CH_2), 2.47 (3H, s, CH_3).

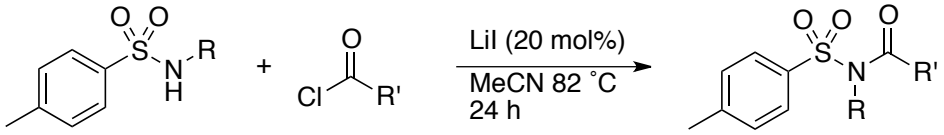
2.18 - *N*-Hexyl-4-methylbenzene sulfonamide[128]



Following representative procedure III, hexylamine (2.6 mL, 20 mmol) was used as the amine species. The title compound was recovered as a white solid (4.955 g, 97%). ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 7.78 (2H, d, *J* = 8.2 Hz, Ar), 7.34 (2H, d, *J* = 8.2 Hz, Ar), 4.39 (1H, t, *J* = 6.5 Hz, NH), 2.96 (2H, q, *J* = 6.5 Hz, CH_2), 2.46 (3H, s, CH_3), 1.47 (2H, m, CH_2), 1.37-1.12 (6H, m, CH_2), 0.94-0.81 (2H, m, CH_3).

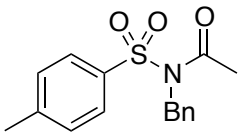
Representative Procedure IV

(Table 2.7, Chapter 2, Section 2.2.2)



To oven dried Radleys carousel tubes lithium iodide and *N*-alkylsulfonamide were added, anhydrous MeCN (2 mL) dissolved the reagents, acid chloride was added to the solution using a micropipette. The tube was then sealed and the reaction mixture was immediately heated to 82 ˚C and stirred for 24 hours. The resulting reaction mixture was then cooled to room temperature and then washed with DCM and sodium thiosulfate solution. The organic components were then dried and concentrated *in vacuo*. The resulting products were analysed by their ^{1}H NMR spectra and mass spectrometry data.

2.19 - *N*-Benzyl-*N*-tosylacetamide[98]



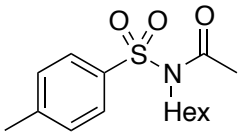
Following representative procedure IV, *N*-benzyl-4-methylbenzene sulfonamide **2.17** (1.307 g, 5 mmol) was used as the *N*-alkylsulfonamide species, acetyl chloride (427 µL, 5 mmol) was used as the acid chloride species and lithium iodide (134 mg, 1 mmol, 20 mol%) was used. The ^{1}H NMR of the crude reaction mixture showed 78%

conversion by comparison of the peaks at 4.15 (2H, d, *J* = 6.0 Hz, CH_2, **2.17**) and 5.11 (2H, s, CH_2, **2.19**). ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 7.64 (2H, d, *J* = 8.4 Hz, Ar), 7.47-7.19 (7H, m, Ar), 5.11 (2H, s, CH_2), 2.45 (3H, s, CH_3), 2.32 (3H, s, CH_3). ESI-MS of [$C_{16}H_{17}NO_3S$]; theoretical m/z of $[M+H]^+$ = 304.1007, measured m/z of $[M+H]^+$ = 304.1005.

Absence of lithium iodide - 2.19 - *N*-benzyl-*N*-tosylacetamide[98]

The ^{1}H NMR of the crude reaction mixture showed 25% conversion by comparison of the peaks at 4.15 (2H, d, *J* = 6.0 Hz, CH_2, **2.17**) and 5.11 (2H, s, CH_2, **2.19**).

2.20 - *N*-Hexyl-*N*-tosylacetamide

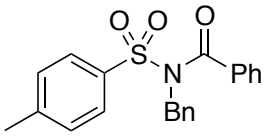


Following representative procedure IV, *N*-hexyl-4-methylbenzene sulfonamide **2.18** (1.277 g, 5 mmol) was used as the *N*-alkylsulfonamide species, acetyl chloride (427 µL, 5 mmol) was used as the acid chloride species and lithium iodide (134 mg, 1 mmol, 20 mol%) was used. The ^{1}H NMR of the crude reaction mixture showed 83% conversion by comparison of the peaks at 2.96 (2H, q, *J* = 6.9 Hz, CH_2, **2.18**) and 3.79 (2H, m, CH_2, **2.20**). ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 7.80 (2H, d, *J* = 8.2 Hz, Ar), 7.37 (2H, d, *J* = 8.2 Hz, Ar), 3.79 (2H, m, CH_2), 2.47 (3H, s, CH_3), 2.34 (3H, s, CH_3), 1.76-1.68 (2H, m, CH_2), 1.42-1.21 (6H, m, CH_2), 0.98-0.81 (3H, m, CH_3). ESI-MS of [$C_{15}H_{23}NO_3S$]; theoretical m/z of $[M+H]^+$ = 298.1477, measured m/z of $[M+H]^+$ = 298.1486.

Absence of lithium iodide - 2.20 - *N*-Hexyl-*N*-tosylacetamide

The ^{1}H NMR of the crude reaction mixture showed 39% conversion by comparison of the peaks at 2.96 (2H, q, *J* = 6.9 Hz, CH_2, **2.18**) and 3.79 (2H, m, CH_2, **2.20**).

2.21 - *N*-Benzyl-*N*-tosylbenzamide

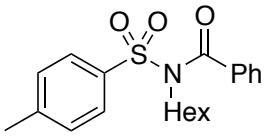


Following representative procedure IV, *N*-benzyl-4-methylbenzene sulfonamide **2.17** (261 mg, 1 mmol) was used as the *N*-alkylsulfonamide species, benzoyl chloride (140 µL, 1.2 mmol) was used as the acid chloride species and lithium iodide (27 mg, 0.2 mmol, 20 mol%) was used. The ^{1}H NMR: ($CDCl_3$, 250 MHz) of the crude reaction mixture showed 3% conversion by comparison of the peaks at 4.16 (2H, d, *J* = 5.1 Hz, CH_2, **2.17**) and 5.33 (2H, s, CH_2, **2.19**).

Absence of lithium iodide - 2.21 - *N*-Benzyl-*N*-tosylbenzamide

The ^{1}H NMR: ($CDCl_3$, 250 MHz) of the crude reaction mixture showed 0% conversion.

2.22 - *N*-Hexyl-*N*-tosylacetamide



Following representative procedure IV, *N*-hexyl-4-methylbenzene sulfonamide **2.18** (255 mg, 1 mmol) was used as the *N*-alkylsulfonamide species, benzoyl chloride (140 µL, 1.2 mmol) was used as the acid chloride species and lithium iodide (27 mg, 0.2 mmol, 20 mol%) was used. The ^{1}H NMR: ($CDCl_3$, 250 MHz) of the crude reaction mixture showed 0% conversion.

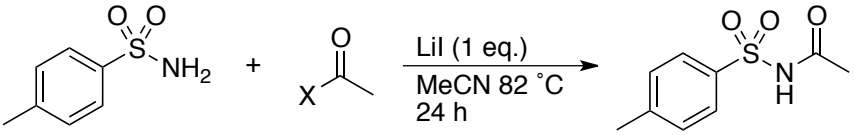
Absence of lithium iodide - 2.22 - *N*-Hexyl-*N*-tosylacetamide

The ^{1}H NMR: ($CDCl_3$, 250 MHz) of the crude reaction mixture showed 0% conversion.

Reactivity of the acid derivative series (Chapter 2, Section 2.2)

Representative Procedure V

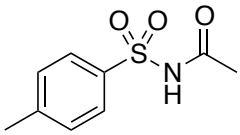
(Table 2.8, Chapter 2, Section 2.2.3)



To oven dried Radleys carousel tubes lithium iodide and *p*-toluenesulfonamide (342 mg, 2 mmol) were added, anhydrous MeCN (2 mL) dissolved the reagents, acid derivative was added to the solution using a micropipette. The tube was then sealed and the reaction mixture was heated to 82 ˚C and stirred for 24 hours. The resulting reaction mixture was then washed with DCM and sodium thiosulfate solution. The organic components were then dried and concentrated *in vacuo*. The resulting products were analysed by their ^{1}H NMR spectra.

Acetic anhydride as the acid derivative

2.4 - *N*-Tosylacetamide[98]



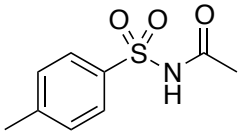
Following representative procedure V, acetic anhydride (227 µL, 2.4 mmol) was used as the acid derivative and lithium iodide (268 mg, 2 mmol, 1 eq.) was used. The ^{1}H NMR of the crude reaction mixture showed 81% conversion. ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 8.73 (1H, br.s, NH), 7.81 (2H, d, *J* = 8.2 Hz, Ar), 7.22 (2H, d, *J* = 8.2 Hz, Ar), 2.32 (3H, s, CH_3), 1.94 (3H, s, CH_3).

Absence of lithium iodide - 2.4 - *N*-Tosylacetamide[98]

The ^{1}H NMR of the crude reaction mixture showed 81% conversion consistent with the data shown above.

_t_-Butyl acetate as the acid derivative

2.4 - _N_-Tosylacetamide[98]



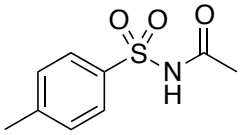
Following representative procedure V, _t_-butyl acetate (324 µL, 2.4 mmol) was used as the acid derivative and lithium iodide (268 mg, 2 mmol, 1 equivalent) was used. The ^{1}H NMR: ($CDCl_3$, 250 MHz) of the crude reaction mixture showed 0% conversion.

Absence of lithium iodide - 2.4 - _N_-Tosylacetamide[98]

The ^{1}H NMR: ($CDCl_3$, 250 MHz) of the crude reaction mixture showed 0% conversion.

Acetic acid as the acid derivative

2.4 - _N_-Tosylacetamide[98]



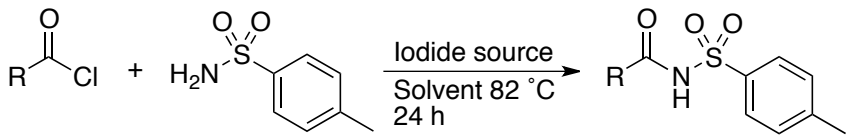
Following representative procedure V, acetic acid (138 µL, 2.4 mmol) was used as the acid derivative and lithium iodide (268 mg, 2 mmol, 1 equivalent) was used. The ^{1}H NMR: ($CDCl_3$, 250 MHz) of the crude reaction mixture showed 0% conversion.

Absence of lithium iodide - 2.4 - _N_-Tosylacetamide[98]

The ^{1}H NMR: ($CDCl_3$, 250 MHz) of the crude reaction mixture showed 0% conversion.

Potassium iodide (Chapter 2, Section 2.3)

Representative Procedure VI



To oven dried Radleys carousel tubes an iodide source or salt (0.2 mmol) and _p_-toluenesulfonamide (171 mg, 1 mmol) were added, 1 mL of anhydrous MeCN dissolved the reagents, acid chloride was added to the solution using a micropipette. The tube was then sealed and the reaction mixture was immediately heated to 82 ˚C

and stirred for 24 hours. The resulting reaction mixture was then cooled to room temperature and washed with DCM and sodium thiosulfate solution. The organic components were then dried and concentrated *in vacuo*. The resulting crude products were analysed by their ^{1}H NMR spectra.

Iodide source screen

(Table 2.9, Chapter 2, Section 2.3.1)

Following representative procedure VI, the appropriate iodide source was used according to Table 2.9 and valeroyl chloride (150 μL, 1.2 mmol) was used as the acid chloride species. The ^{1}H NMR of the crude reaction mixture showed % conversion by comparison of the peaks at 7.94 (2H, d, *J* = 8.2 Hz, Ar) and 7.83 (2H, d, *J* = 8.3 Hz, Ar).

Other salts

(Table 2.10, Chapter 2, Section 2.3.1)

Following representative procedure VI, the appropriate salt was used according to Table 2.10 and valeroyl chloride (150 μL, 1.2 mmol) was used as the acid chloride species. The ^{1}H NMR of the crude reaction mixture showed % conversion into **2.11** by comparison of the peaks at 7.94 (2H, d, *J* = 8.2 Hz, Ar, **2.11**) and 7.83 (2H, d, *J* = 8.3 Hz, Ar).

Iodide source screen

(Table 2.11, Chapter 2, Section 2.3.1)

Following representative procedure VI, the appropriate iodide source was used according to Table 2.11 and benzoyl chloride (140 μL, 1.2 mmol) was used as the acid chloride species. The ^{1}H NMR of the crude reaction mixture showed % conversion by comparison of the peaks at 7.97 (2H, d, *J* = 8.3 Hz, Ar, **2.10**) and 5.83 (4H, s, CH_2 2,5-dimethylfuran).

Variation of potassium iodide loading

(Table 2.12, Chapter 2, Section 2.3.1)

Following representative procedure VI, the appropriate amount of potassium iodide was used according to Table 2.12 and benzoyl chloride (140 μL, 1.2 mmol) was used as the acid chloride species. The ^{1}H NMR of the crude reaction mixture showed % conversion by comparison of the peaks at 7.97 (2H, d, *J* = 8.3 Hz, Ar, **2.10**) and 5.83 (4H, s, CH_2 2,5-dimethylfuran).

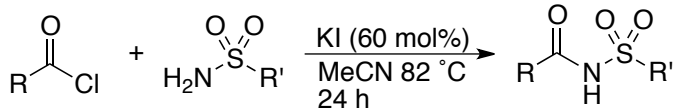
Solvent screen

(Table 2.13, Chapter 2, Section 2.3.1)

Following representative procedure VI, potassium iodide (99.6 mg, 0.6 mmol, 60 mol%) was used as the iodide source, the appropriate solvent was used according to Table 2.13 and benzoyl chloride (140 μL, 1.2 mmol) was used as the acid chloride species. The ^{1}H NMR of the crude reaction mixture showed % conversion by comparison of the peaks at 7.97 (2H, d, *J* = 8.3 Hz, Ar, **2.10**) and 5.83 (4H, s, CH_2 2,5-dimethylfuran).

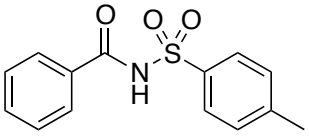
Representative Procedure VII

(Table 2.14 & 2.15, Chapter 2, Section 2.3.1)



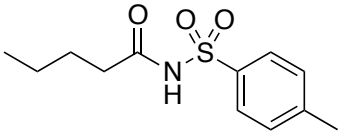
To oven dried Radleys carousel tubes potassium iodide (99.6 mg, 0.6 mmol, 60 mol%) and sulfonamide were added, 1 mL of anhydrous MeCN dissolved the reagents, acid chloride was added to the solution using a micropipette. The tube was then sealed and the reaction mixture was immediately heated to 82 ˚C and stirred for 24 hours. The resulting reaction mixture was then cooled to room temperature and washed with DCM and sodium thiosulfate solution. The organic components were then dried and concentrated *in vacuo*. Purification by either column chromatography or recrystallization was carried out as necessary. The resulting products were analysed by their ^{1}H and ^{13}C NMR spectra and mass spectrometry data.

2.23 - *N*-Tosylbenzamide[123]



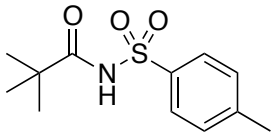
Following representative procedure VII, *p*-toluenesulfonamide (514 mg, 3 mmol) was used as the sulfonamide species and benzoyl chloride (418 µL, 3.6 mmol) as the acid chloride species. The title compound was recovered as an off-white solid (739 mg, 89% yield) after column chromatography eluting with 3:1 Hexane/EtOAc. ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 9.36 (1H, br.s, NH), 7.97 (2H, d, *J* = 8.3 Hz, Ar), 7.75 (2H, d, *J* = 8.6 Hz, Ar), 7.56-7.40 (1H, m, Ar), 7.34 (2H, t, *J* = 7.6 Hz, Ar), 7.27 (2H, d, *J* = 8.3 Hz, Ar), 2.36 (3H, s, CH_3). ^{13}C NMR: ($CDCl_3$, 75.5 MHz) δ 164.4, 145.3, 135.5, 133.5, 131.1, 129.7, 129.7, 128.7, 127.9, 21.75. IR (film, cm^{-1}): ν_{max} = 1703 (C=O). ESI-MS of [$C_{14}H_{13}NO_3S$]; theoretical m/z of $[M-H]^-$ = 274.0537, measured m/z of $[M-H]^-$ = 274.0537.

2.24 - *N*-Tosylpentanamide[48]



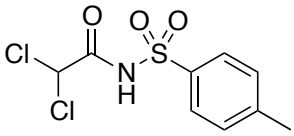
Following representative procedure VII, *p*-toluenesulfonamide (514 mg, 3 mmol) was used as the sulfonamide species and valeroyl chloride (434 µL, 3.6 mmol) as the acid chloride species. The title compound was recovered as an off-white solid (676 mg, 88% yield) after column chromatography eluting with 3:1 Hexane/EtOAc. ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 9.13 (1H, br.s, NH), 7.94 (2H, d, *J* = 8.2 Hz, Ar), 7.34 (2H, d, *J* = 8.2 Hz, Ar), 2.43 (3H, s, CH_3), 2.31-2.20 (2H, m, CH_2), 1.52 (2H, m, CH_2), 1.24 (2H, m, CH_2), 0.82 (3H, t, *J* = 7.3 Hz, CH_3). ^{13}C NMR: ($CDCl_3$, 75.5 MHz) δ 171.5, 145.2, 135.6, 129.7, 128.3, 36.0, 26.3, 22.0, 21.7, 13.7. IR (film, cm^{-1}): ν_{max} = 1704 (C=O). ESI-MS of [$C_{12}H_{17}NO_3S$]; theoretical m/z of $[M-H]^-$ = 254.0850, measured m/z of $[M-H]^-$ = 254.0854.

2.25 - *N*-Tosylpivalamide[123]



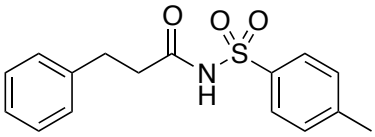
Following representative procedure VII, *p*-toluenesulfonamide (514 mg, 3 mmol) was used as the sulfonamide species and pivaloyl chloride (445 µL, 3.6 mmol) as the acid chloride species. The title compound was recovered as an off-white solid (614 mg, 80% yield) after column chromatography eluting with 3:1 Hexane/EtOAc. ^{1}H NMR: ($CDCl_3$, 300 MHz) ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 8.74 (1H, br.s, NH), 7.88 (2H, d, *J* = 8.2 Hz, Ar), 7.27 (2H, d, *J* = 8.2 Hz, Ar), 2.37 (3H, s, CH_3), 1.07 (9H, s, CH_3). ^{13}C NMR: ($CDCl_3$, 75.5 MHz) δ 176.2, 145.0, 135.5, 129.6, 128.4, 40.0, 26.7, 21.7. IR (film, cm^{-1}): ν_{max} = 1708 (C=O). ESI-MS of [$C_{12}H_{17}NO_3S$]; theoretical m/z of $[M-H]^-$ = 254.0851, measured m/z of $[M-H]^-$ = 254.0846.

2.26 - *N*-Tosyldichloroacetamide[124]



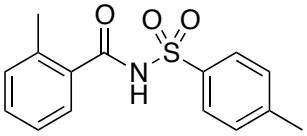
Following representative procedure VII, *p*-toluenesulfonamide (514 mg, 3 mmol) was used as the sulfonamide species and dichloroacetyl chloride (577 µL, 6 mmol) was used as the acid chloride species. The title compound was recovered as an off-white solid (344 mg, 41% yield) after column chromatography eluting with 1:1 Hexane/EtOAc. ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 9.03 (1H, br.s, NH), 7.90 (2H, d, *J* = 8.3 Hz, Ar), 7.31 (2H, d, *J* = 8.3 Hz, Ar), 5.78 (1H, s, CH), 2.39 (3H, s, CH_3). ^{13}C NMR: ($CDCl_3$, 75.5 MHz) δ 160.9, 146.1, 134.1, 129.9, 128.7, 65.6, 21.8. IR (film, cm^{-1}): ν_{max} = 1706 (C=O). ESI-MS of [$C_9H_9{}^{35}Cl_2NO_3S$]; theoretical m/z of $[M+Na]^+$ = 303.9578, measured m/z of $[M+Na]^+$ = 303.9584.

2.27 - *N*-Tosylhydrocinnamide[125]



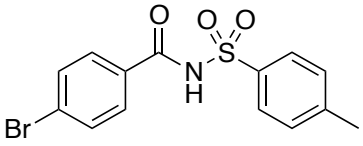
Following representative procedure VII, *p*-toluenesulfonamide (514 mg, 3 mmol) was used as the sulfonamide species and hydrocinnamoyl chloride (535 µL, 3.6 mmol) as the acid chloride species. The title compound was recovered as a pale yellow solid (829 mg, 91% yield) after column chromatography eluting with 3:1 Hexane/EtOAc. ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 9.03 (1H, br.s, NH), 7.89 (2H, d, *J* = 8.3 Hz, Ar), 7.31 (2H, d, *J* = 8.3 Hz, Ar), 7.25-7.13 (3H, m, Ar), 7.06 (2H, m, Ar), 2.86 (2H, t, *J* = 7.7 Hz, CH_2), 2.56 (2H, t, *J* = 7.7 Hz, CH_2), 2.45 (3H, s, CH_3). ^{13}C NMR: ($CDCl_3$, 75.5 MHz) δ 170.5, 145.2, 139.7, 135.4, 129.7, 128.6, 128.4, 128.3, 126.4, 37.9, 30.3, 21.8. IR (film, cm^{-1}): ν_{max} = 1680 (C=O). ESI-MS of [$C_{16}H_{17}NO_3S$]; theoretical m/z of $[M-H]^-$ = 302.0851, measured m/z of $[M-H]^-$ = 302.0855.

2.28 - *N*-Tosyl-*o*-toluamide[50]



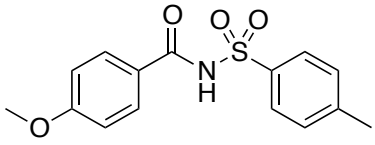
Following representative procedure VII, *p*-toluenesulfonamide (514 mg, 3 mmol) was used as the sulfonamide species and *o*-toluoyl chloride (470 µL, 3.6 mmol) as the acid chloride species. The title compound was recovered as an off-white solid (800 mg, 92% yield) after column chromatography eluting with 3:1 Hexane/EtOAc. ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 8.75 (1H, br.s, NH), 7.93 (2H, d, *J* = 8.0 Hz, Ar), 7.39-7.21 (4H, m, Ar), 7.12(2H, d, *J* = 8.0 Hz, Ar), 2.37 (3H, s, CH_3), 2.27 (3H, s, CH_3). ^{13}C NMR: ($CDCl_3$, 75.5 MHz) δ 166.3, 145.2, 138.0, 135.5, 132.1, 131.8, 131.7, 129.7, 128.5, 127.3, 126.0, 21.8, 20.1. IR (film, cm^{-1}): ν_{max} = 1698 (C=O). ESI-MS of [$C_{15}H_{15}NO_3S$]; theoretical m/z of $[M-H]^-$ = 288.0694, measured m/z of $[M-H]^-$ = 288.0688.

2.29 - 4-Bromo-*N*-tosylbenzamide[50]



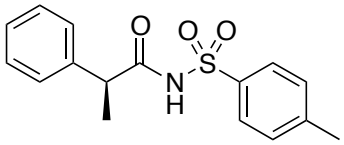
Following representative procedure VII, *p*-toluenesulfonamide (514 mg, 3 mmol) was used as the sulfonamide species and 4-bromobenzoyl chloride (790 mg, 3.6 mmol) as the acid chloride species. The title compound was recovered as a grey solid (711 mg, 67% yield) after column chromatography eluting with 3:1 Hexane/EtOAc. ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 9.09 (1H, br.s, NH), 8.03 (2H, d, *J* = 8.2 Hz, Ar), 7.66 (2H, d, *J* = 8.8 Hz, Ar), 7.58 (2H, d, *J* = 8.8 Hz, Ar), 7.36 (2H, d, *J* = 8.2 Hz, Ar), 2.45 (3H, s, CH_3). ^{13}C NMR: ($CDCl_3$, 75.5 MHz) δ 163.4, 145.5, 135.3, 132.3, 130.1, 129.7, 129.3, 128.7, 126.5, 21.7. IR (film, cm^{-1}): ν_{max} = 1703 (C=O). ESI-MS of [$C_{14}H_{12}{}^{79}BrNO_3S$]; theoretical m/z of $[M-H]^-$ = 351.9643, measured m/z of $[M-H]^-$ = 351.9649.

2.30 - 4-Methoxy-*N*-tosylbenzamide[125]



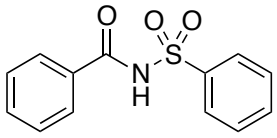
Following representative procedure VII, *p*-toluenesulfonamide (514 mg, 3 mmol) was used as the sulfonamide species and 4-methoxybenzoyl chloride (487 µL, 3.6 mmol) as the acid chloride species. The title compound was recovered as a pale yellow solid (893 mg, 97% yield) after column chromatography eluting with 9:1 Hexane/EtOAc. ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 9.28 (1H, br.s, NH), 8.04 (2H, d, *J* = 8.3 Hz, Ar), 7.79 (2H, d, *J* = 8.9 Hz, Ar), 7.34 (2H, d, *J* = 8.3 Hz, Ar), 6.89 (2H, d, *J* = 8.9 Hz, Ar), 3.82 (3H, s, CH_3), 2.43 (3H, s, CH_3). ^{13}C NMR: ($CDCl_3$, 75.5 MHz) δ 163.8, 145.1, 135.6, 130.1, 129.6, 129.6, 128.6, 123.3, 114.2, 55.6, 21.7. IR (film, cm^{-1}): ν_{max} = 1766 (C=O). ESI-MS of [$C_{15}H_{15}NO_4S$]; theoretical m/z of $[M+H]^+$ = 306.0800, measured m/z of $[M+H]^+$ = 306.0781.

2.31 - (S)-2-Phenyl-*N*-tosylpropanamide



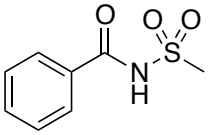
Following representative procedure VII, *p*-toluenesulfonamide (171 mg, 1 mmol) was used as the sulfonamide species and (s)-2-phenylpropoyl chloride (205 µL, 1.2 mmol, >99% enantiomeric excess) as the acid chloride species. The title compound was recovered as an off-white solid (164 mg, 54% yield, 80% enantiomeric excess) after preparative chiral HPLC. ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 8.17 (1H, br.s, NH), 7.72 (2H, d, *J* = 8.2 Hz, Ar), 7.19 (5H, d, *J* = 6.2 Hz, Ar), 7.00 (2H, d, *J* = 8.2 Hz, Ar), 3.48 (1H, q, CH_3), 2.37 (3H, s, CH_3), 1.30 (3H, s, CH_3). ^{13}C NMR: ($CDCl_3$, 75.5 MHz) δ 171.5, 145.1, 139.0, 135.2, 130.0, 129.3, 128.4, 127.9, 127.6, 47.4, 21.7, 18.0. IR (film, cm^{-1}): ν_{max} = 1709 (C=O). ESI-MS of [$C_{16}H_{17}NO_3S$]; theoretical m/z of $[M-H]^-$ = 302.0851, measured m/z of $[M-H]^-$ = 302.0841.

2.32 - *N*-Benzenesulfonamide benzoyl[48]



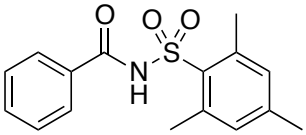
Following representative procedure VII, benzenesulfonamide (471 mg, 3 mmol) was used as the sulfonamide species and benzoyl chloride (418 µL, 3.6 mmol) as the acid chloride species. The title compound was recovered as a yellow solid (752 mg, 96% yield) after column chromatography eluting with 2:1 Hexane/EtOAc. ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 9.10 (1H, br.s, NH), 8.10 (2H, d, *J* = 7.1 Hz, Ar), 7.73 (2H, d, *J* = 7.1 Hz, Ar), 7.59 (1H, 1, *J* = 7.5 Hz, Ar), 7.49 (3H, t, *J* = 7.5 Hz, Ar), 7.36 (2H, t, *J* = 7.5 Hz, Ar). ^{13}C NMR: ($CDCl_3$, 75.5 MHz) δ 164.2, 138.5, 134.1, 133.6, 131.1, 129.0, 129.0, 128.6, 127.8. IR (film, cm^{-1}): ν_{max} = 1694 (C=O). ESI-MS of [$C_{13}H_{11}NO_3S$]; theoretical m/z of $[M-H]^-$ = 260.0381, measured m/z of $[M-H]^-$ = 260.0374.

2.33 - *N*-Benzoyl-methanesulfonamide[99]



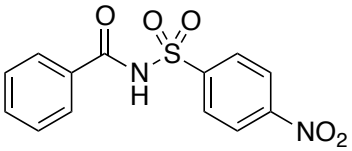
Following representative procedure VII, methanesulfonamide (285 mg, 3 mmol) was used as the sulfonamide species and benzoyl chloride (418 µL, 3.6 mmol) as the acid chloride species. The title compound was recovered as a white solid (496 mg, 83% yield) recrystallized after layering hexane on DCM solution. ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 8.98 (1H, br.s, NH), 7.81 (2H, d, *J* = 7.4 Hz, Ar), 7.56 (1H, t, *J* = 7.4 Hz, Ar), 7.43 (2H, t, *J* = 7.4 Hz, Ar), 3.37 (3H, s, CH_3). ^{13}C NMR: ($CDCl_3$, 75.5 MHz) δ 165.5, 133.9, 130.9, 129.1, 127.9, 41.8. IR (film, cm^{-1}): ν_{max} = 1678 (C=O). ESI-MS of [$C_8H_9NO_3S$]; theoretical m/z of $[M-H]^-$ = 198.0225, measured m/z of $[M-H]^-$ = 198.0228.

2.34 - *N*-Benzoyl-2,4,6-trimethylbenzenesulfonamide



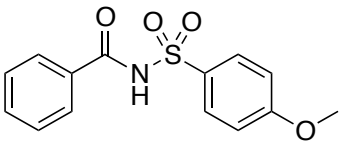
Following representative procedure VII, 2,4,6-trimethylbenzenesulfonamide (598 mg, 3 mmol) was used as the sulfonamide species and benzoyl chloride (418 µL, 3.6 mmol) as the acid chloride species. The title compound was recovered as a pale yellow solid (664 mg, 73% yield) after column chromatography eluting with 8:1 Hexane/EtOAc, mp 174-176 ˚C, ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 9.41 (1H, br.s, NH), 7.76 (2H, m, Ar), 7.50 (1H, t, *J* = 8.0 Hz, Ar), 7.37 (2H, t, *J* = 8.0 Hz, Ar), 6.93 (2H, s, Ar), 2.71 (6H, s, CH_3); 2.23 (3H, s, CH_3). ^{13}C NMR: ($CDCl_3$, 75.5 MHz) δ 164.8, 143.9, 140.7, 133.5, 132.2, 131.2, 129.0, 129.0, 127.8, 22.9, 21.1. IR (film, cm^{-1}): ν_{max} = 2986, 1696 (C=O), 1600, 1452, 1337, 1156, 1054, 708. ESI-MS of [$C_{16}H_{17}NO_3S$]; theoretical m/z of $[M-H]^-$ = 304.34, measured m/z of $[M-H]^-$ = 304.2 Requires C 63.34%; H 5.65%; N 4.62%, found: C 63.40%; H 5.66%; N 4.49%

2.35 - *N*-Benzoyl *N*-4-nitro-benzenesulfonamide[50]



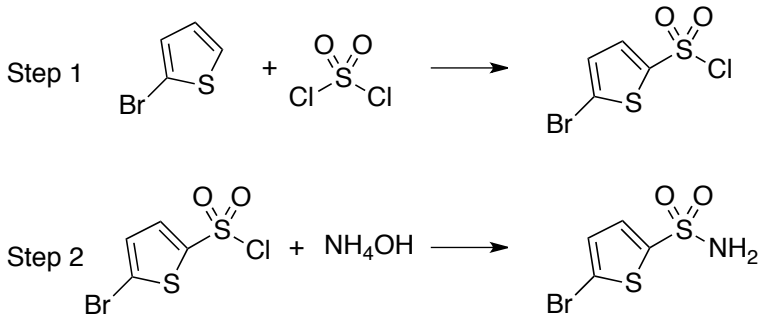
Following representative procedure VII, 4-nitrobenzenesulfonamide (607 mg, 3 mmol) was used as the sulfonamide species and benzoyl chloride (418 µL, 3.6 mmol) as the acid chloride species. The title compound was recovered as a pale yellow solid (716 mg, 78% yield) after column chromatography eluting with 3:1 Hexane/EtOAc. ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 9.00 (1H, br.s, NH), 8.39-8.24 (4H, m, Ar), 7.71 (2H, d, *J* = 7.2 Hz, Ar), 7.47-7.32 (3H, m, Ar). ^{13}C NMR: ($CDCl_3$, 75.5 MHz) δ 164.2, 148.8, 134.1, 130.2, 129.2, 127.8, 127.7, 124.2, 114.6. IR (film, cm^{-1}): ν_{max} = 1692 (C=O). ESI-MS of [$C_{13}H_{10}N_2O_5S$]; theoretical m/z of $[M-H]^-$ = 305.0304, measured m/z of $[M-H]^-$ = 305.0302.

2.36 - *N*-Benzoyl *N*-4-methoxy-benzenesulfonamide[99]



Following representative procedure VII, 4-methoxybenzenesulfonamide (562 mg, 3 mmol) was used as the sulfonamide species and benzoyl chloride (418 µL, 3.6 mmol) as the acid chloride species. The title compound was recovered as a pale yellow solid (728 mg, 83% yield) after column chromatography eluting with 9:1 Hexane/EtOAc. ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 9.32 (1H, br.s, NH), 8.10 (2H, d, *J* = 9.1 Hz, Ar), 7.82 (2H, d, *J* = 7.4 Hz, Ar), 7.55 (1H, m, Ar), 7.42 (2H, t, *J* = 7.4 Hz, Ar), 7.01 (2H, d, *J* = 9.1 Hz, Ar), 3.87 (3H, s, CH_3). ^{13}C NMR: ($CDCl_3$, 75.5 MHz) δ 164.4, 164.1, 133.5, 131.2, 131.1, 129.7, 128.9, 127.8, 114.2, 55.8. IR (film, cm^{-1}): ν_{max} = 1695 (C=O). ESI-MS of [$C_{14}H_{13}NO_4S$]; theoretical m/z of $[M-H]^-$ = 290.0487, measured m/z of $[M-H]^-$ = 290.0479.

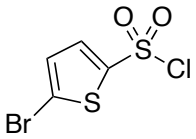
Synthesis of 2.38 - 5-bromothiophene-2-sulfonamide[99, 129]



Step 1: DMF (3 mL, 39 mmol) was added to a flask and cooled to 0 ˚C, in an ice bath, sulfonyl chloride (3.16 mL, 39 mmol) was added dropwise to the cooled DMF, maintaining the temperature below 25 ˚C. A precipitate formed after 10 minutes and was held at <25 ˚C for 30 minutes. 2-bromothiophene (2.9 mL, 30 mmol) was added to the DMF-SO_2Cl_2 complex and the mixture was immediately heated to 98 ˚C for one hour. The viscous brown mixture was cooled to room temperature and added to ice-water and subsequently extracted with $CHCl_3$. Then a subsequent aqueous extraction with 5% lithium chloride solution and DCM was performed to remove excess DMF. The organic components were then dried and concentrated *in vacuo* and subsequently purified by bulb-to-bulb distillation *in vacuo* bp 95-100 ˚C/1 Torr affording 5-bromothiophene-2-sulfonylchloride **2.37** as a yellow oil.

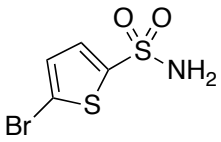
Step 2: 5-bromothiophene-2-sulfonylchloride **2.37** (3.1235 g, 11.94 mmol) and 2-methyltetrahydrofuran (30 mL, solvent) were combined under argon in a flask forming a light yellow solution. The solution was cooled to 0 ˚C in an ice bath. Concentrated aqueous NH_4OH (250 mL, 48 mmol, 5 *N*) was added dropwise to the reaction over 30 minutes. The reaction was allowed to warm to room temperature and stirred overnight. The reaction mixture was then diluted with 100 mL DI water. The pH of the reaction mixture was then adjusted to pH <6 using 37% conc. aq HCL. The phases were separated and the aqueous layer was back extracted with 2-methyltetrahydrofuran (3 X 10 mL) and subsequently washed with brine (3 X 10 mL). The organic components were then dried and concentrated *in vacuo* to afford 5-bromothiophene-2-sulfonamide **2.38** as a beige solid.

2.37 – 5-Bromothiophene-2-sulfonylchloride[129]



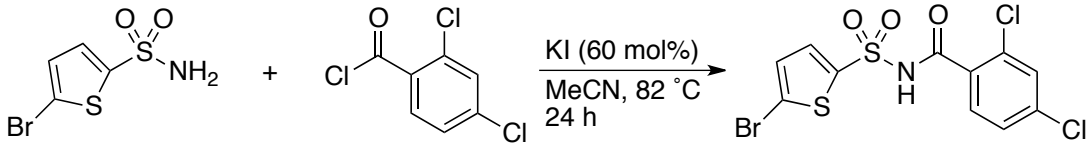
The title compound was recovered as a pale yellow oil (3.1235 g, 40% yield). ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 7.58 (1H, d, *J* = 4.2 Hz, Ar), 7.10 (1H, d, *J* = 4.2 Hz, Ar).

2.38 – 5-Bromothiophene-2-sulfonamide[99]



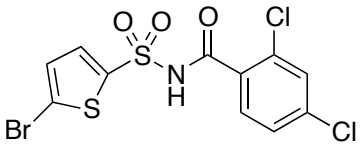
The title compound was recovered as a beige solid (2.579 g, 89% yield). ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 7.45 (1H, d, *J* = 4.0 Hz, Ar), 7.09 (1H, d, *J* = 4.0 Hz, Ar), 5.10 (2H, br.s, NH_2). ^{13}C NMR: ($CDCl_3$, 75.5 MHz) δ 146.9, 131.3, 131.0, 117.2. ESI-MS of [$C_4H_4{}^{79}BrNO_2S_2$]; theoretical m/z of $[M-H]^-$ = 239.8789, measured m/z of $[M-H]^-$ = 239.8793.

Synthesis of *N*-((5-bromothiophen-2-yl)sulfonyl)-2,4-dichlorobenzamide 2.39[99]



To oven dried Radleys carousel tubes potassium iodide (199.2 mg, 1.2 mmol, 60 mol%) and 5-bromothiophene-2-sulfonamide (484 mg, 2 mmol, **2.38**) were added, 1 mL of anhydrous MeCN dissolved the reagents, 2,4-dichlorobenzoyl chloride (336 μL, 2.4 mmol) was added to the solution using a micropipette. The tube was then sealed and the reaction mixture was immediately heated to 82 ˚C and stirred for 24 hours. The resulting reaction mixture was then cooled to room temperature and washed with DCM and sodium thiosulfate solution. The organic components were then dried and concentrated *in vacuo*. Purification by column chromatography 3:1 Hexane/EtOAc. The resulting products were analysed by their ^{1}H and ^{13}C NMR spectra and mass spectrometry data.

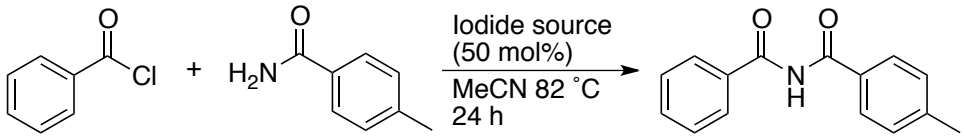
2.39 – *N*-((5-Bromothiophen-2-yl)sulfonyl)-2,4-dichlorobenzamide[99]



The title compound was recovered as a white solid (0.1584 g, 19% yield). ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 8.99 (1H, br.s, NH), 7.70 (1H, d, *J* = 8.5 Hz, Ar), 7.67 (1H, d, *J* = 4.1 Hz, Ar), 7.40 (1H, s, Ar), 7.32 (2H, m, Ar), 7.07 (1H, d, *J* = 4.1 Hz, Ar). ^{13}C NMR: ($CDCl_3$, 75.5 MHz) δ 164.5, 139.9, 136.2, 135.1, 132.4, 131.3, 131.2, 130.6, 129.5, 127.5, 121.1. ESI-MS of $[C_{11}H_6{}^{79}Br{}^{35}Cl_2NO_3S_2]$; theoretical m/z of $[M+Na]^+$ = 435.8247, measured m/z of $[M+Na]^+$ = 435.8257.

Amides (Chapter 2, Section 2.3.2)

Representative Procedure VII



To oven dried Radleys carousel tubes an iodide source (0.5 mmol, 50 mol%) and *p*-toluamide (135 mg, 1 mmol) were added, 1 mL of anhydrous MeCN dissolved the reagents, benzoyl chloride (140 μL, 1.2 mmol) was added to the solution using a micropipette. The tube was then sealed and the reaction mixture was immediately heated to 82 ˚C and stirred for 24 hours. The resulting reaction mixture was then cooled to room temperature and washed with DCM and sodium thiosulfate solution. The organic components were then dried and concentrated *in vacuo*. The resulting crude products were analysed by their ^{1}H and ^{13}C NMR spectra against an internal standard of 2,5-dimethylfuran (0.5 mmol).

Iodide source screen

(Table 2.16, Chapter 2, Section 2.3.2)

Following representative procedure VII, the appropriate iodide source was used according to Table 2.16. The ^{1}H NMR of the crude reaction mixture showed % conversion by comparison of the peaks at 7.86 (2H, d, *J* = 8.6 Hz, Ar, **2.40**) and 5.75 (4H, s, CH_2 2,5-dimethylfuran). ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 8.93 (1H, br.s, NH), 7.86

(2H, d, *J* = 8.6 Hz, Ar), 7.77 (2H, d, *J* = 8.1 Hz, Ar), 7.66-7.43 (3H, m, Ar), 7.30 (2H, d, *J* = 8.1 Hz, Ar), 2.43 (3H, s, CH_3). ^{13}C NMR: ($CDCl_3$, 75.5 MHz) δ 166.5, 166.2, 144.1, 133.5, 133.1, 130.5, 129.6, 128.9, 128.0, 127.9, 21.7.

Variation of potassium iodide loading

(Table 2.17, Chapter 2, Section 2.3.2)

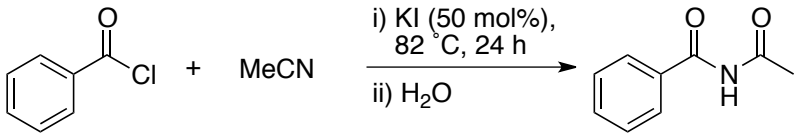
Following representative procedure VII, the appropriate amount of potassium iodide was used according to Table 2.17. The ^1H NMR of the crude reaction mixture showed % conversion by comparison of the peaks at 7.86 (2H, d, *J* = 8.6 Hz, Ar, **2.40**) and 5.75 (4H, s, CH_2 2,5-dimethylfuran).

Variation of acid chloride and potassium iodide amount

(Table 2.18, Chapter 2, Section 2.3.2)

Following representative procedure VII, the appropriate amount of potassium iodide and benzoyl chloride was used according to Table 2.18. The ^1H NMR of the crude reaction mixture showed % conversion by comparison of the peaks at 7.86 (2H, d, *J* = 8.6 Hz, Ar, **2.40**) and 5.75 (4H, s, CH_2 2,5-dimethylfuran).

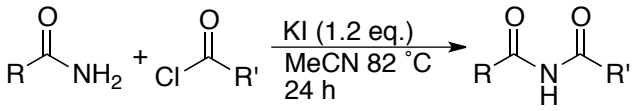
Competing pathway



To oven dried Radleys carousel tubes potassium iodide (83 mg, 0.5 mmol, 50 mol%) and MeCN (52 µL, 1 mmol) were added, benzoyl chloride (116 µL, 1 mmol) was added to the solution using a micropipette. The tube was then sealed and the reaction mixture was immediately heated to 82 ˚C and stirred for 24 hours. The resulting reaction mixture was then cooled to room temperature and washed with DCM and sodium thiosulfate solution. The organic components were then dried and concentrated *in vacuo*. The ^1H NMR: ($CDCl_3$, 250 MHz) of the crude reaction mixture showed 5% conversion into **2.41** by comparison of the peaks at 7.95 (2H, d, *J* = 8.5 Hz, Ar, **2.41**) and 5.75 (4H, s, CH_2 2,5-dimethylfuran).

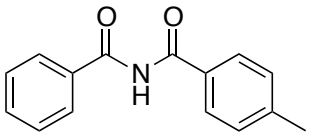
Representative Procedure VIII

(Table 2.19 & 2.20, Chapter 2, Section 2.3.2)



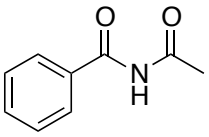
To oven dried Radleys carousel tubes potassium iodide (498 mg, 3 mmol, 1.2 eq.) and amide were added, 3 mL of anhydrous MeCN dissolved the reagents, acid chloride was added to the solution using a micropipette. The tube was then sealed and the reaction mixture was immediately heated to 82 ˚C and stirred for 24 hours. The resulting reaction mixture was then cooled to room temperature and washed with DCM and sodium thiosulfate solution. The organic components were then dried and concentrated *in vacuo*. The resulting crude products were analysed by their ^{1}H and ^{13}C NMR spectra and mass spectrometry data.

2.40 - *N*-Benzoyl-4-methybenzamide[130] (Table 2.19, entry 1)



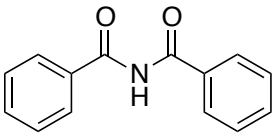
Following representative procedure VIII, benzamide (606 mg, 5 mmol) was used as the amide species and *p*-toluoyl chloride (1.587 mL, 12 mmol) as the acid chloride species. The ^{1}H NMR of the crude reaction mixture showed 100% conversion into **2.40** by comparison of the peaks at 7.86 (2H, d, *J* = 8.6 Hz, Ar, **2.40**) and 5.75 (4H, s, CH_2 2,5-dimethylfuran). ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 8.93 (1H, br.s, NH), 7.86 (2H, d, *J* = 8.6 Hz, Ar), 7.77 (2H, d, *J* = 8.1 Hz, Ar), 7.66-7.43 (3H, m, Ar), 7.30 (2H, d, *J* = 8.1 Hz, Ar), 2.43 (3H, s, CH_3). ^{13}C NMR: ($CDCl_3$, 75.5 MHz) δ 166.5, 166.2, 144.1, 133.5, 133.1, 130.5, 129.6, 128.9, 128.0, 127.9, 21.7. ESI-MS of [$C_{15}H_{13}NO_2$]; theoretical m/z of $[M+H]^+$ = 240.1014, measured m/z of $[M+H]^+$ = 240.1025.

2.41 - *N*-Benzoylacetamide[130] (Table 2.19, entry 2)



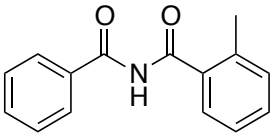
Following representative procedure VIII, benzamide (606 mg, 5 mmol) was used as the amide species and acetyl chloride (853 μL, 12 mmol) as the acid chloride species. The ^{1}H NMR of the crude reaction mixture showed 100% conversion into **2.41** by comparison of the peaks at 2.54 (3H, s, CH_3, **2.41**) and 5.75 (4H, s, CH_2 2,5-dimethylfuran). ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 9.19 (1H, br.s, NH), 7.83 (2H, d, *J* = 7.1 Hz, Ar), 7.62-7.36 (3H, m, Ar), 2.54 (3H, s, CH_3).

2.42 - *N*-Benzoylbenzamide[131]



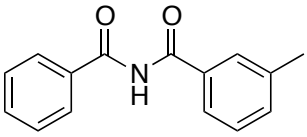
Following representative procedure VIII, benzamide (606 mg, 5 mmol) was used as the amide species and benzoyl chloride (1.384 mL, 12 mmol) as the acid chloride species. The ^{1}H NMR of the crude reaction mixture showed 100% conversion into **2.42** by comparison of the peaks at 7.91 (2H, d, *J* = 7.3 Hz, Ar) and 5.75 (4H, s, CH_2 2,5-dimethylfuran). ^{1}H NMR: ($CDCl_3$, 250 MHz) δ 9.66 (1H, br.s, NH), 7.91 (4H, d, *J* = 7.3 Hz, Ar), 7.79-7.36 (6H, m, Ar).

2.43 - *N*-(2-Methylbenzoyl)benzamide[132]



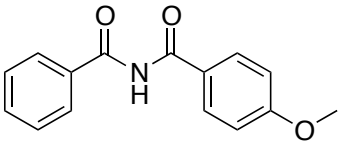
Following representative procedure VIII, benzamide (606 mg, 5 mmol) was used as the amide species and 2-methylbenzoyl chloride (1.565 mL, 12 mmol) as the acid chloride species. The ^{1}H NMR of the crude reaction mixture showed 100% conversion into **2.43** by comparison of the peaks at 7.90 (2H, d, *J* = 7.2 Hz, Ar) and 5.87 (4H, s, CH_2 2,5-dimethylfuran). ^{1}H NMR: ($CDCl_3$, 250 MHz) δ 8.89 (1H, br.s, NH), 7.90 (2H, d, *J* = 7.2 Hz, Ar), 7.69-7.25 (7H, m, Ar), 2.52 (3H, s, CH_3).

2.44 - *N*-(3-Methylbenzoyl)benzamide[133]



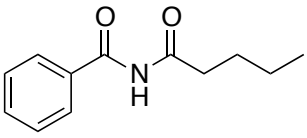
Following representative procedure VIII, benzamide (606 mg, 5 mmol) was used as the amide species and 3-methylbenzoyl chloride (1.198 mL, 12 mmol) as the acid chloride species. The ^{1}H NMR of the crude reaction mixture showed 100% conversion into **2.44** by comparison of the peaks at 7.96 (2H, d, *J* = 8.5 Hz, Ar) and 5.75 (4H, s, CH_2 2,5-dimethylfuran). ^{1}H NMR: (DMSO, 250 MHz) δ 9.46 (1H, br.s, NH), 7.96 (2H, d, *J* = 8.5 Hz, Ar), 7.81-7.71 (2H, m, Ar), 7.56-7.31 (5H, m, Ar), 2.37 (3H, s, CH_3).

2.45 - *N*-(4-Methoxybenzoyl)benzamide[134]



Following representative procedure VIII, benzamide (606 mg, 5 mmol) was used as the amide species and 4-methoxybenzoyl chloride (1.625 mL, 12 mmol) as the acid chloride species. The ^{1}H NMR of the crude reaction mixture showed 58% conversion into **2.45** by comparison of the peaks at 7.88 (2H, d, *J* = 8.3 Hz, Ar) and 5.84 (4H, s, CH_2 2,5-dimethylfuran). ^{1}H NMR: ($CDCl_3$, 250 MHz) δ 9.54 (1H, br.s, NH), 8.07 (2H, d, *J* = 8.9 Hz, Ar), 7.88 (2H, d, *J* = 8.3 Hz, Ar), 7.70-7.37 (3H, m, Ar), 6.97 (2H, d, *J* = 8.9 Hz, Ar), 3.85 (3H, s, CH_3).

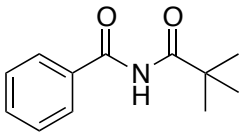
2.46 – *N*-Pentanoylbenzamide[132]



Following representative procedure VIII, benzamide (606 mg, 5 mmol) was used as the amide species and valeroyl chloride (1.424 mL, 12 mmol) as the acid chloride species. The ^{1}H NMR of the crude reaction mixture showed 100% conversion into **2.46** by comparison of the peaks at 7.90 (2H, d, *J* = 8.6 Hz, Ar) and 5.78 (4H, s, CH_2

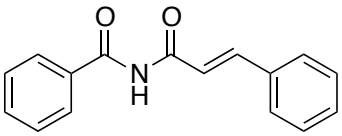
2,5-dimethylfuran). ^{1}H NMR: ($CDCl_3$, 250 MHz) δ 9.70 (1H, br.s, NH), 7.90 (2H, d, *J* = 8.6, Ar), 7.65-7.35 (3H, m, Ar), 2.90 (2H, t, *J* = 7.4 Hz, CH_2), 1.75-1.47 (2H, m, CH_2), 1.47-1.19 (2H, m, CH_2), 0.97-0.81 (3H, m, CH_3).

2.47 - *N*-Pivaloylbenzamide[135]



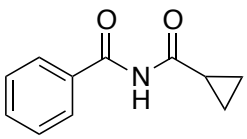
Following representative procedure VIII, benzamide (606 mg, 5 mmol) was used as the amide species and trimethylacetyl chloride (1.478 mL, 12 mmol) as the acid chloride species. The ^{1}H NMR of the crude reaction mixture showed 66% conversion into **2.47** by comparison of the peaks at 7.77 (2H, d, *J* = 7.0 Hz, Ar) and 5.84 (4H, s, CH_2 2,5-dimethylfuran). ^{1}H NMR: ($CDCl_3$, 250 MHz) δ 8.63 (1H, br.s, NH), 7.77 (2H, d, *J* = 7.0 Hz, Ar), 7.67-7.43 (3H, m, Ar), 1.35 (9H, s, CH_3).

2.48 – (*E*)-*N*-Cinnamoylbenzamide[136]



Following representative procedure VIII, benzamide (606 mg, 5 mmol) was used as the amide species and cinnamoyl chloride (1.999 g, 12 mmol) as the acid chloride species. The ^{1}H NMR of the crude reaction mixture showed 48% conversion into **2.48** by comparison of the peaks at 7.97 (2H, d, *J* = 8.7 Hz, Ar) and 5.86 (4H, s, CH_2 2,5-dimethylfuran). ^{1}H NMR: ($CDCl_3$, 250 MHz) δ 9.90 (1H, br.s, NH), 7.97 (2H, d, *J* = 8.7, Ar), 7.69-7.36 (8H, m, Ar), 6.63 (2H, d, *J* = 15.6 Hz, HC=CH).

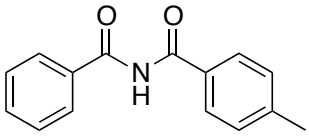
2.49 - *N*-(Cyclopropanecarbonyl)benzamide[137]



Following representative procedure VIII, benzamide (606 mg, 5 mmol) was used as the amide species and cyclopropanecarbonyl chloride (1.089 mL, 12 mmol) as the

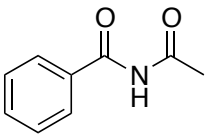
acid chloride species. The ^{1}H NMR of the crude reaction mixture showed 58% conversion into **2.49** by comparison of the peaks at 7.89 (2H, d, *J* = 4.9 Hz, Ar) and 5.86 (4H, s, CH_2 2,5-dimethylfuran). ^{1}H NMR: ($CDCl_3$, 250 MHz) δ 9.57 (1H, br.s, NH), 7.89 (2H, d, *J* = 4.9 Hz, Ar), 7.54-7.43 (3H, m, Ar), 2.55-2.40 (1H, m, CH), 1.06-0.83 (4H, m, CH_2).

2.40 - *N*-Benzoyl-4-methybenzamide[130] (Table 2.20, entry 1)



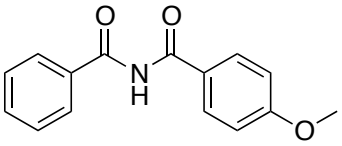
Following representative procedure VIII, *p*-toluamide (676 mg, 5 mmol) was used as the sulfonamide species and benzoyl chloride (1.384 mL, 12 mmol) as the acid chloride species. The ^{1}H NMR of the crude reaction mixture showed 79% conversion into **2.40** by comparison of the peaks at 7.86 (2H, d, *J* = 8.6 Hz, Ar, **2.40**) and 5.75 (4H, s, CH_2 2,5-dimethylfuran). ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 8.93 (1H, br.s, NH), 7.86 (2H, d, *J* = 8.6 Hz, Ar), 7.77 (2H, d, *J* = 8.1 Hz, Ar), 7.66-7.43 (3H, m, Ar), 7.30 (2H, d, *J* = 8.1 Hz, Ar), 2.43 (3H, s, CH_3). ^{13}C NMR: ($CDCl_3$, 75.5 MHz) δ 166.5, 166.2, 144.1, 133.5, 133.1, 130.5, 129.6, 128.9, 128.0, 127.9, 21.7. ESI-MS of [$C_{15}H_{13}NO_2$]; theoretical m/z of $[M+H]^+$ = 240.1014, measured m/z of $[M+H]^+$ = 240.1025.

2.41 - *N*-Benzoylacetamide[130] (Table 2.20, entry 2)



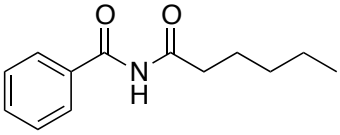
Following representative procedure VIII, acetamide (296 mg, 5 mmol) was used as the amide species and benzoyl chloride (1.384 mL, 12 mmol) as the acid chloride species. The ^{1}H NMR of the crude reaction mixture showed 66% conversion into **2.41** by comparison of the peaks at 2.54 (3H, s, CH_3, **2.41**) and 5.75 (4H, s, CH_2 2,5-dimethylfuran). ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 9.19 (1H, br.s, NH), 7.83 (2H, d, *J* = 7.1 Hz, Ar), 7.62-7.36 (3H, m, Ar), 2.54 (3H, s, CH_3).

2.50 - *N*-(4-Methoxybenzoyl)benzamide[134]



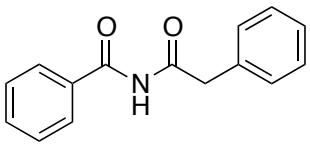
Following representative procedure VIII, 4-methoxybenzamide (756 mg, 5 mmol) was used as the amide species and benzoyl chloride (1.384 mL, 12 mmol) as the acid chloride species. The ^{1}H NMR of the crude reaction mixture showed 70% conversion into **2.50** by comparison of the peaks at 7.88 (2H, d, *J* = 8.3 Hz, Ar) and 5.84 (4H, s, CH_2 2,5-dimethylfuran). ^{1}H NMR: ($CDCl_3$, 250 MHz) δ 9.54 (1H, br.s, NH), 8.07 (2H, d, *J* = 8.9, Ar), 7.88 (2H, d, *J* = 8.3 Hz, Ar), 7.70-7.37 (3H, m, Ar), 6.97 (2H, d, *J* = 8.9 Hz, Ar), 3.85 (3H, s, CH_3).

2.51 – *N*-Hexanoylbenzamide[138]



Following representative procedure VIII, hexamide (576 mg, 5 mmol) was used as the amide species and benzoyl chloride (1.384 mL, 12 mmol) as the acid chloride species. The ^{1}H NMR of the crude reaction mixture showed 75% conversion into **2.51** by comparison of the peaks at 7.96 (2H, d, *J* = 7.4 Hz, Ar) and 5.84 (4H, s, CH_2 2,5-dimethylfuran). ^{1}H NMR: ($CDCl_3$, 250 MHz) δ 9.60 (1H, br.s, NH), 7.96 (2H, d, *J* = 7.4, Ar), 7.66-7.39 (3H, m, Ar), 3.02 (2H, t, *J* = 7.5 Hz, CH_2), 1.65 (2H, q, *J* = 7.5 Hz, CH_2), 1.50-1.25 (2H, m, CH_2), 0.93 (3H, t, *J* = 7.1 Hz, CH_3).

2.52 - *N*-(2-Phenylacetyl)benzamide[135]

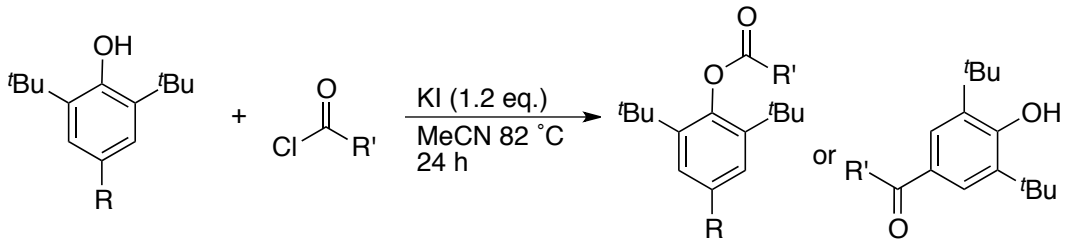


Following representative procedure VIII, 2-phenylacetamide (676 mg, 5 mmol) was used as the amide species and benzoyl chloride (1.384 mL, 12 mmol) as the acid chloride species. The ^{1}H NMR of the crude reaction mixture showed 80% conversion into **2.52** by comparison of the peaks at 7.80 (2H, d, *J* = 7.1 Hz, Ar) and 5.84 (4H, s,

CH_2 2,5-dimethylfuran). ^{1}H NMR: ($CDCl_3$, 250 MHz) δ 9.09 (1H, br.s, NH), 7.80 (2H, d, *J* = 7.1, Ar), 7.63-7.49 (1H, m, Ar), 7.47-7.35 (2H, m, Ar), 7.33-7.10 (5H, m, Ar), 3.58 (2H, s, CH_2).

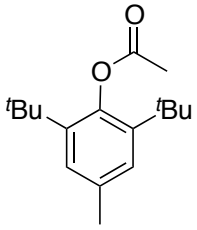
Other nucleophiles (Chapter 2, Section 2.3.3)

Representative Procedure IX



To oven dried Radleys carousel tubes potassium iodide (598 mg, 3.6 mmol) and a hindered phenol (3 mmol) were added, 3 mL of anhydrous MeCN dissolved the reagents, acid chloride (7.2 mmol) was added to the solution using a micropipette. The tube was then sealed and the reaction mixture was immediately heated to 82 ˚C and stirred for 24 hours. The resulting reaction mixture was then cooled to room temperature and washed with DCM and sodium thiosulfate solution. The organic components were then dried and concentrated *in vacuo*. Purification by either column chromatography or recrystallization was carried out as necessary.

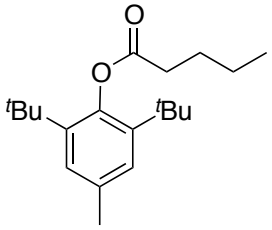
2.53 - 2,6-Di-*tert*-butyl-4-methylphenyl acetate[139]



Following representative procedure IX, 2,6-di-*tert*-butyl-4-methylphenol (661 mg, 3 mmol) as the hindered phenol and acetyl chloride (510 µL, 7.2 mmol) as the acid chloride species. The title compound was recovered as a yellow solid (746 mg, 95% yield) after column chromatography eluting with 99:1 Hexane/EtOAc. ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 7.17-7.12 (2H, m, Ar), 2.36 (3H, s, CH_3), 2.35 (3H, s, CH_3), 1.37 (18H, s, CH_3). ^{13}C NMR: ($CDCl_3$, 75.5 MHz) δ 171.4, 145.7, 142.0, 134.6, 127.1, 35.3,

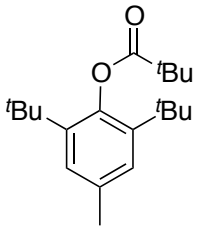
31.5, 22.7, 21.6. IR (film, cm^{-1}): ν_{max} = 1759 (C=O). ESI-MS of [$C_{17}H_{26}O_2$]; theoretical m/z of $[M+H]^+$ = 285.1831, measured m/z of $[M+H]^+$ = 285.1829.

2.54 - 2,6-Di-*tert*-butyl-4-methylphenyl pentanoate



Following representative procedure IX, 2,6-di-*tert*-butyl-4-methylphenol (661 mg, 3 mmol) as the hindered phenol and valeroyl chloride (855 µL, 7.2 mmol) as the acid chloride species. The title compound was recovered as a yellow oil (882 mg, 97% yield) after column chromatography eluting with 99:1 Hexane/EtOAc. ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 7.12 (2H, s, Ar), 2.68-2.53 (2H, m, CH_2), 2.32 (3H, s, CH_3), 1.76 (2H, m, CH_2), 1.46 (2H, m, CH_2), 1.33 (18H, s, CH_3), 0.98 (3H, t, *J* = 7.3 Hz, CH_3). ^{13}C NMR: ($CDCl_3$, 75.5 MHz) δ 173.8, 145.9, 142.0, 134.4, 127.0 Hz, 35.2, 31.5, 30.2, 26.4, 22.4, 21.6, 13.8. IR (film, cm^{-1}): ν_{max} = 1758 (C=O). ESI-MS of [$C_{17}H_{32}O_2$]; theoretical m/z of $[M+H]^+$ = 305.2481, measured m/z of $[M+H]^+$ = 305.2485. C H N requires C 78.90%; H 10.59%; N 0%, found: C 78.60%; H 10.50%; N 0%

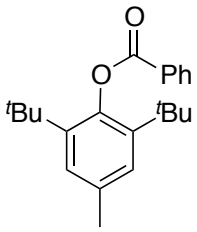
2.55 - 2,6-Di-*tert*-butyl-4-methylphenyl pivalate[140]



Following representative procedure IX, 2,6-di-*tert*-butyl-4-methylphenol (661 mg, 3 mmol) as the hindered phenol and pivaloyl chloride (890 µL, 7.2 mmol) as the acid chloride species. The title compound was recovered as a yellow solid (493 mg, 54% yield) after column chromatography eluting with 99:1 Hexane/EtOAc. ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 7.13 (2H, s, Ar), 2.34 (3H, s, CH_3), 1.40 (9H, s, CH_3), 1.35 (18H, s, CH_3). ^{13}C NMR: ($CDCl_3$, 75.5 MHz) δ 177.4, 147.7, 140.6, 134.8, 127.8, 127.4, 123.5,

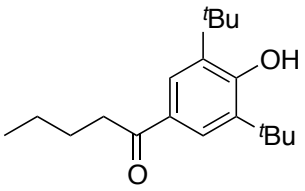
30.1, 27.3, 21.2. ESI-MS of [$C_{20}H_{32}O_2$]; theoretical m/z of $[M+Na]^+$ = 327.2300, measured m/z of $[M+Na]^+$ = 327.2314.

2.56 - 2,6-Di-*tert*-butyl-4-methylphenyl benzoate[141]



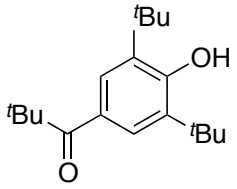
Following representative procedure IX, 2,6-di-*tert*-butyl-4-methylphenol (661 mg, 3 mmol) as the hindered phenol and benzoyl chloride (835 µL, 7.2 mmol) as the acid chloride species. The title compound was recovered as a yellow oil (504 mg, 52% yield) after column chromatography eluting with 99:1 Hexane/EtOAc. ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 8.24 (2H, d, *J* = 8.5 Hz, Ar), 7.72-7.45 (3H, m, Ar), 7.17 (2H, s, Ar), 2.28 (3H, s, CH_3), 1.44 (18H, s, CH_3). ^{13}C NMR: ($CDCl_3$, 75.5 MHz) δ 171.9, 151.5, 135.7, 130.3, 128.7, 128.7, 128.3, 125.6, 123.9, 34.3, 30.3, 21.2. ESI-MS of [$C_{22}H_{28}O_2$]; theoretical m/z of $[M+H]^+$ = 325.2124, measured m/z of $[M+H]^+$ = 325.2105.

2.57 - 1-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)pentan-1-one[142]



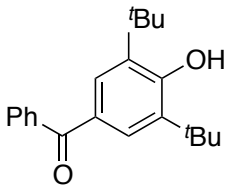
Following representative procedure IX, 2,6-di-*tert*-butyl-phenol (617 mg, 3 mmol) as the hindered phenol and valeroyl chloride (855µL, 7.2 mmol) as the acid chloride species. The title compound was recovered as a yellow oil (847mg, 97% yield) after column chromatography eluting with 99:1 Hexane/EtOAc. ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 7.87 (2H, s, Ar), 5.62 (1H, s, OH), 2.94 – 2.76, (2H, m, CH_2COAr), 2.68 - 2.49 (2H, m, CH_2), 1.29 (20H, m, (18H)CH_3, (2H)CH_2), 0.94 – 0.90 (3H, m, CH_3). ^{13}C NMR: ($CDCl_3$, 75.5 MHz) δ 200.2, 173.1, 143.1, 134.0, 126.4, 38.2, 35.6, 31.3, 26.2, 22.5, 14.0. IR (film, cm^{-1}): ν_{max} = 3054 (OH), 1761 (C=O). ESI-MS of [$C_{19}H_{30}O_2$]; theoretical m/z of $[M-H]^-$ = 289.2168, measured m/z of $[M-H]^-$ = 289.2181.

2.58 - 1-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-2,2-dimethylpropan-1-one[143]



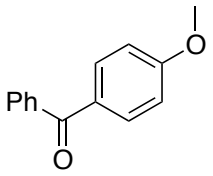
Following representative procedure IX, 2,6-di-*tert*-butyl-phenol (617 mg, 3 mmol) as the hindered phenol and pivaloyl chloride (890 µL, 7.2 mmol) as the acid chloride species. The title compound was recovered as a yellow oil (502 mg, 58% yield) after column chromatography eluting with 99:1 Hexane/EtOAc. ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 7.72 (2H, s, Ar), 5.54 (1H, s, OH), 1.39 (18H, s, CH_3), 1.31 (9H, s, CH_3). ^{13}C NMR: ($CDCl_3$, 75.5 MHz) δ 206.8, 157.0 Hz, 128.5, 126.7, 43.7, 34.4, 30.2, 28.7. IR (film, cm^{-1}): ν_{max} = 3062 (OH), 1748 (C=O). ESI-MS of [$C_{19}H_{30}O_2$]; theoretical m/z of $[M-H]^-$ = 289.2200, measured m/z of $[M-H]^-$ = 289.2194.

2.59 - (3,5-Di-*tert*-butyl-4-hydroxyphenyl)(phenyl)methanone[143]



Following representative procedure IX, 2,6-di-*tert*-butyl-phenol (617 mg, 3 mmol) as the hindered phenol and benzoyl chloride (835 µL, 7.2 mmol) as the acid chloride species. The title compound was recovered as a yellow oil (280 mg, 30% yield) after column chromatography eluting with 99:1 Hexane/EtOAc. ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 7.77 (2H, d, *J* = 8.0, Ar), 7.72 (2H, s, Ar), 7.58-7.44 (3H, m, Ar), 5.74 (1H, s, OH), 1.44 (18H, s, CH_3). ^{13}C NMR: ($CDCl_3$, 75.5 MHz) δ 206.8, 157.0 Hz, 135.7, 130.3, 128.7, 128.5, 128.3, 126.7 125.6, 123.9, 30.2, 28.7. IR (film, cm^{-1}): ν_{max} = 3114 (OH), 1749 (C=O). ESI-MS of [$C_{21}H_{26}O_2$]; theoretical m/z of $[M-H]^-$ = 309.1900, measured m/z of $[M-H]^-$ = 309.1930.

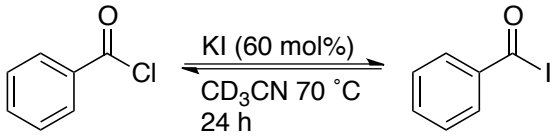
2.60 - (4-Methoxyphenyl)(phenyl)methanone[144]



Following representative procedure IX, anisole (110 μL, 1 mmol) as the electron-rich aromatic and benzoyl chloride (140 μL, 1.2 mmol) as the acid chloride species. The title compound was recovered as a yellow oil (75 mg, 35% yield) after column chromatography eluting with 99:1 Hexane/EtOAc. ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 7.85-7.82 (2H, m, Ar), 7.76-7.74 (2H, m, Ar), 7.58-7.45 (3H, m, Ar), 6.98-6.95 (2H, m, Ar), 3.88 (3H, s, CH_3). ^{13}C NMR: ($CDCl_3$, 75.5 MHz) δ 195.6, 163.2, 138.3, 132.6, 131.9, 130.1, 129.8, 128.2, 113.6, 55.5. IR (film, cm^{-1}): ν_{max} = 1758 (C=O). ESI-MS of [$C_{14}H_{12}O_2$]; theoretical m/z of $[M+H]^+$ = 213.2651, measured m/z of $[M+H]^+$ = 213.2678.

Mechanistic investigations (Chapter 2, Section 2.4)

Representative Procedure X



To an oven dried NMR tube potassium iodide (99.6 mg, 0.6 mmol, 60 mol%) or appropriate iodide source was added, 1 mL of anhydrous CD_3CN dissolved the reagent, benzoyl chloride (140 μL, 1.2 mmol) was added to the solution using a micropipette. The tube was then sealed and the reaction mixture was immediately placed in the pre-heated NMR machine at 70 ˚C. ^{13}C NMR spectra were then taken every 30 minutes over 24 hours.

2.61 - Benzoyl iodide formation experiment[100]

Following representative procedure X. ^{13}C NMR spectra were then taken every 30 minutes over 24 hours. The ^{13}C NMR spectra showed relative % conversion by comparison of the peaks at 168.6 (benzoyl chloride, C=O) and 159.6 (benzoyl iodide, C=O, **2.61**).

Relative % conversion of benzoyl chloride into benzoyl iodide 2.61

(Figure 2.1, Chapter 2, Section 2.4)

Following representative procedure X. ^{13}C NMR spectra were then taken every 30 minutes over 24 hours. The ^{13}C NMR spectra showed relative % conversion by comparison of the peaks at 168.6 (benzoyl chloride, C=O) and 159.6 (benzoyl iodide, C=O, **2.61**). The relative integrations were calculated for each spectrum and the figures plotted in the graph shown in Figure 2.1.

2.61 - Benzoyl iodide formation experiment[100]

Following representative procedure X. ^{13}C NMR spectra were then taken every 30 minutes over 24 hours. The ^{13}C NMR spectra showed relative % conversion by comparison of the peaks at 168.6 (benzoyl chloride, C=O) and 159.6 (benzoyl iodide, C=O, **2.61**).

2.61 - Benzoyl iodide formation experiment[100]

Following representative procedure X, tetrabutylammonium iodide (221.3 mg, 0.6 mmol, 60 mol%) was added as the iodide source. ^{13}C NMR spectra were then taken every 30 minutes over 24 hours. The ^{13}C NMR spectra showed no conversion by the absence of a peak at 159.6 (benzoyl iodide, C=O, **2.61**).

Other salts

(Table 2.23, Chapter 2, Section 2.4)

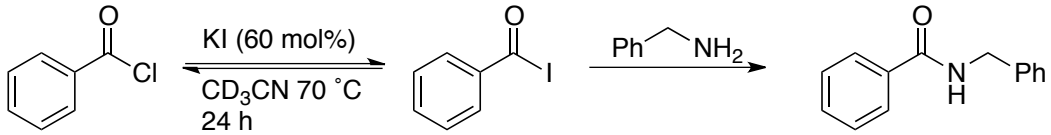
Following representative procedure VII, the appropriate salt was used according to Table 2.23 and benzoyl chloride (140 μL, 1.2 mmol) was used as the acid chloride species. The ^{1}H NMR of the crude reaction mixture showed % conversion by comparison of the peaks at 7.97 (2H, d, *J* = 8.0 Hz, Ar, **2.10**) and 5.83 (4H, s, CH_2 2,5-dimethylfuran).

Crown ether sequestration experiment

(Table 2.24, Chapter 2, Section 2.4)

Following representative procedure VII, the appropriate crown ether (1.32 mmol, 2.2 eq.) was used according to Table 2.24, potassium iodide (99.6 mg, 0.6 mmol, 60 mol%) was used as the iodide source and benzoyl chloride (140 μL, 1.2 mmol) was used as the acid chloride species. The ^{1}H NMR of the crude reaction mixture showed % conversion by comparison of the peaks at 7.97 (2H, d, *J* = 8.0 Hz, Ar, **2.10**) and 5.83 (4H, s, CH_2 2,5-dimethylfuran).

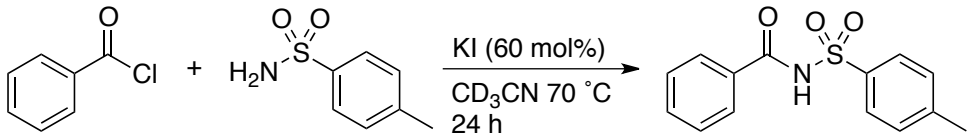
Benzoyl iodide in the presence of a nucleophile



To an oven dried NMR tube potassium iodide (99.6 mg, 0.6 mmol, 60 mol%) was added, 1 mL of anhydrous CD_3CN dissolved the reagent, benzoyl chloride (140 μL, 1.2 mmol) was added to the solution using a micropipette. The tube was then sealed and the reaction mixture was immediately placed in the pre-heated NMR machine at 70 ˚C. The NMR tube was spun for 3 hours, ^{13}C NMR spectra confirmed the presence of ~20% benzoyl iodide **2.61** by comparison of the peaks at 168.6 (benzoyl chloride, C=O) and 159.6 (benzoyl iodide, C=O, **2.61**). The NMR tube was removed from the NMR machine and immediately benzylamine (0.2 mmol) was added, the tube was returned to the NMR machine and analysis by ^{13}C NMR was performed. The ^{13}C NMR spectra showed there was no peak at 159.6 (benzoyl iodide, C=O, **2.61**). However there was a peak at 168.6 (benzoyl chloride, C=O). The NMR tube was again spun for 3 hours, ^{13}C NMR spectra confirmed the presence of ~20% benzoyl iodide **2.61** by comparison of the peaks at 168.6 (benzoyl chloride, C=O) and 159.6 (benzoyl iodide, C=O, **2.61**).

Benzoyl iodide formation in the presence of sulfonamide

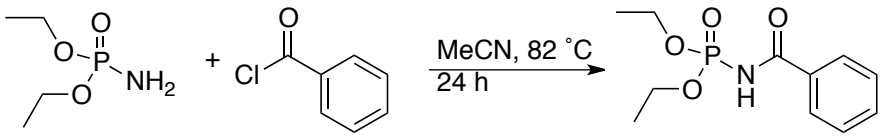
(Scheme 2.14, Chapter 2, Section 2.4)



To an oven dried NMR tube potassium iodide (99.6 mg, 0.6 mmol, 60 mol%) was added, 1 mL of anhydrous CD_3CN dissolved the reagent, benzoyl chloride (140 μL, 1.2 mmol) was added to the solution using a micropipette. The tube was then sealed and the reaction mixture was immediately placed in the pre-heated NMR machine at 70 ˚C. ^{13}C NMR spectra were then taken every 30 minutes over 24 hours. ^{13}C NMR spectra confirmed no formation of benzoyl iodide **2.61** by comparison of the peaks at 168.6 (benzoyl chloride, C=O) and 159.6 (benzoyl iodide, C=O, **2.61**). After 24 hours the NMR tube was spun for 3 hours, ^{13}C NMR spectra confirmed the presence of ~20% benzoyl iodide **2.61** by comparison of the peaks at 168.6 (benzoyl chloride, C=O) and 159.6 (benzoyl iodide, C=O, **2.61**).

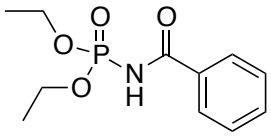
Future work, other nucleophiles

(Scheme 2.15, Chapter 2, Section 2.6)



To oven dried Radleys carousel tubes potassium iodide (99.6 mg, 0.6 mmol, 60 mol%) and diethylphosphoramidate (153 mg, 1 mmol) were added, anhydrous MeCN (2 mL) dissolved the reagents, benzoyl chloride (140 μL, 1.2 mmol) was added to the solution using a micropipette. The tube was then sealed and the reaction mixture was heated to 82 ˚C and stirred for 24 hours. The resulting reaction mixture was then washed with DCM and sodium thiosulfate solution. The organic components were then dried and concentrated *in vacuo*. The resulting products were analysed by their ^{1}H NMR spectra.

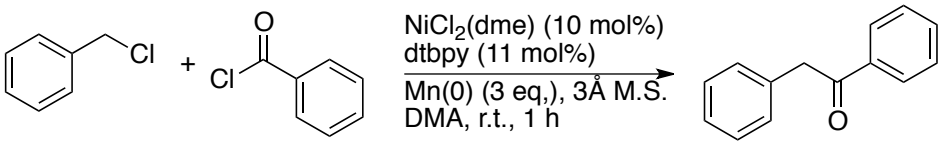
2.62 – Diethyl benzoylphosphoramidate[145]



The ^{1}H NMR: ($CDCl_3$, 250 MHz) of the crude reaction mixture showed % conversion into **2.62** by comparison of the peaks at 7.77 (2H, d, *J* = 6.8 Hz, Ar) and 5.74 (4H, s, CH_2 2,5-dimethylfuran).

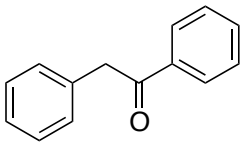
Reisman coupling[103a]

(Scheme 2.16, Chapter 2, Section 2.6)



To oven dried Youngs tubes, were appropriate potassium iodide according to Scheme 2.16, Mn(0) (165 mg, 3 mmol, 3 eq.), $NiCl_2$(dme) (22 mg, 0.1 mmol, 10 mol%), dtbpy (27 mg, 0.11 mmol, 11 mol%) and 3 Å molecular sieves (30 mg) were added and purged under argon for 10 minutes. Anhydrous DMA (2 mL) dissolved the reagents, benzyl chloride (82.3 μL, 1 mmol) and benzoyl chloride (140 μL, 1.2 mmol) was added to the solution using a micropipette. The tube was then sealed and the reaction mixture was stirred at room temperature for 1 hour. The resulting reaction mixture was then transferred to a separating funnel using 1 M HCl (25 mL) and Et_2O (50 mL). The mixture was diluted with H_2O (50 mL) and the aqueous and organic layers separated. The combined organic layers were washed with brine (1 x 50 mL). The organic components were then dried and concentrated *in vacuo*. The resulting products were analysed by their ^{1}H NMR spectra.

2.63 – 1,2-Diphenylethanone[146]

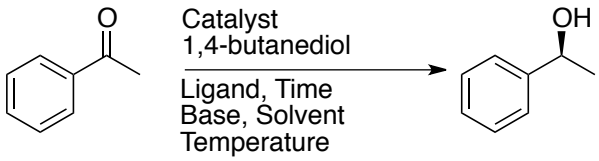


The ^{1}H NMR: ($CDCl_3$, 250 MHz) of the crude reaction mixture showed % conversion into **2.63** by comparison of the peaks at 4.63 (2H, s, CH_2, benzyl chloride) and 4.20 (2H, s, CH_2 **2.63**).

5.3 Chapter 3 Experimental Methods

Representative Procedure XI

(Chapter 3, Section 3.2)



To oven dried Youngs carousel tubes base, catalyst and ligand were added and purged under argon for 10 minutes, 1 mL of anhydrous solvent dissolved the reagents, 1,4-butanediol and acetophenone (117 μL, 1.0 mmol) were added to the solution using a micropipette. The tube was then sealed and the reaction mixture was immediately heated to the appropriate temperature and stirred for the appropriate amount of time. The resulting reaction mixture was then cooled to room temperature and extracted with DCM and water. The organic components were then dried and concentrated *in vacuo*. The resulting crude products were analyzed by their ^{1}H NMR spectra and then purified by column chromatography and enantiomeric excesses determined by HPLC analysis (Daicel Chiracel OD, 10% *i*-PrOH/hexane, 0.5 mL/min).

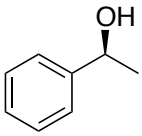
Solvent Screen

(Table 3.1 – Chapter 3, Section 3.2)

Following representative procedure XI, the appropriate anhydrous solvent (1 mL) was used according to Table 3.1, Cs_2CO_3 (33 mg, 0.1 mmol, 10 mol%) was used as the base, $[Ru(p\text{-cymene})Cl_2]_2$ (15 mg, 0.025 mmol, 5 mol%) was used as the catalyst, (*S,S*)-TsDpen (18 mg, 0.05 mmol, 5 mol%) was used as the ligand, 1,4-butanediol (45

μL, 0.5 mmol) was added and the reaction was performed at 30 ˚C and stirred for 24 hours. The ^{1}H NMR and HPLC analysis were consistent with **3.1**.

3.1 – (*S*)-1-Phenylethanol



^{1}H NMR: ($CDCl_3$, 250 MHz) δ 7.47-7.24 (5H, m, Ar), 4.91 (1H, q, *J* = 6.5 Hz, CHOH), 1.51 (3H, d, *J* = 6.5 Hz CH_3). HPLC analysis: Daicel Chiracel OD, 10% *i*-PrOH/hexane, 0.5 mL/min; t_R 10.40 R, 12.94 S.

Varying catalyst and ligand loading

(Table 3.2, Chapter 3, Section 3.2)

Following representative procedure XI, toluene (1 mL) was used as the solvent, Cs_2CO_3 (33 mg, 0.1 mmol, 10 mol%) was used as the base, [Ru(*p*-cymene)Cl_2]$_2$ was used as appropriate according to Table 3.2, (*S,S*)-TsDpen was used as appropriate according to Table 3.2, 1,4-butanediol (45 μL, 0.5 mmol) was added and the reaction was performed at 30 ˚C and stirred for 24 hours. The ^{1}H NMR and HPLC analysis were consistent with **3.1**.

Varying temperature, reaction time and concentration in solvent

(Table 3.3, Chapter 3, Section 3.2)

Following representative procedure XI, toluene (1 mL) was used as the solvent, Cs_2CO_3 (33 mg, 0.1 mmol, 10 mol%) was used as the base, [Ru(*p*-cymene)Cl_2]$_2$ (15 mg, 0.025 mmol, 5 mol%) was used as the catalyst, (*S,S*)-TsDpen (18 mg, 0.05 mmol, 5 mol%) was used as the ligand, 1,4-butanediol (45 μL, 0.5 mmol) was added and the reaction was performed at the appropriate temperature and for the appropriate amount of time according to Table 3.3. The ^{1}H NMR and HPLC analysis were consistent with **3.1**.

Varying base with PhMe as the solvent

(Chapter 3, Section 3.2)

Following representative procedure XI, toluene (1 mL) was used as the solvent, the appropriate base was used according to the text, $[Ru(p\text{-cymene})Cl_2]_2$ (15 mg, 0.025 mmol, 5 mol%) was used as the catalyst, (*S,S*)-TsDpen (18 mg, 0.05 mmol, 5 mol%) was used as the ligand, 1,4-butanediol (45 μL, 0.5 mmol) was added and the reaction was performed at 30 ˚C and stirred for 1 hour. The ^{1}H NMR and HPLC analysis were consistent with **3.1**.

Varying base with 9:1 THF/H_2O as the solvent

(Table 3.4, Chapter 3, Section 3.2)

Following representative procedure XI, 9:1 THF/H_2O (0.5 mL) was used as the solvent, the appropriate base was used according to Table 3.4, $[Ru(p\text{-cymene})Cl_2]_2$ (15 mg, 0.025 mmol, 5 mol%) was used as the catalyst, (*S,S*)-TsDpen (18 mg, 0.05 mmol, 5 mol%) was used as the ligand, 1,4-butanediol (45 μL, 0.5 mmol) was added and the reaction was performed at 30 ˚C and stirred for 1 hour. The ^{1}H NMR and HPLC analysis were consistent with **3.1**.

Repeating to check consistency

(Table 3.5, Chapter 3, Section 3.2)

Following representative procedure XI, 9:1 THF/H_2O (0.5 mL) was used as the solvent, KOH (5.6 mg, 0.1 mmol, 10 mol%) was used as the base, $[Ru(p\text{-cymene})Cl_2]_2$ (15 mg, 0.025 mmol, 5 mol%) was used as the catalyst, (*S,S*)-TsDpen (18 mg, 0.05 mmol, 5 mol%) was used as the ligand, 1,4-butanediol (45 μL, 0.5 mmol) was added and the reaction was performed at 30 ˚C and stirred for 1 hour. The ^{1}H NMR and HPLC analysis were consistent with **3.1**.

Varying amount of KOH

(Table 3.6, Chapter 3, Section 3.2)

Following representative procedure XI, 9:1 THF/H_2O (0.5 mL) was used as the solvent, the appropriate amount of KOH was used according to Table 3.6, [Ru(*p*-cymene)Cl_2]$_2$ (15 mg, 0.025 mmol, 5 mol%) was used as the catalyst, (*S,S*)-TsDpen (18 mg, 0.05 mmol, 5 mol%) was used as the ligand, 1,4-butanediol (45 μL, 0.5 mmol) was added and the reaction was performed at 30 ˚C and stirred for 1 hour. The ^{1}H NMR and HPLC analysis were consistent with **3.1**.

Varying amount of 1,4-butanediol

(Table 3.7, Chapter 3, Section 3.2)

Following representative procedure XI, 9:1 THF/H_2O (0.5 mL) was used as the solvent, KOH (17 mg, 0.3 mmol, 30 mol%) was used as the base, [Ru(*p*-cymene)Cl_2]$_2$ (15 mg, 0.025 mmol, 5 mol%) was used as the catalyst, (*S,S*)-TsDpen (18 mg, 0.05 mmol, 5 mol%) was used as the ligand, the appropriate amount of 1,4-butanediol was added according to Table 3.7 and the reaction was performed at 30 ˚C and stirred for 1 hour. The ^{1}H NMR analysis was consistent with **3.1**.

Reaction in the presence of γ-butyrolactone

(Chapter 3, Section 3.2)

Following representative procedure XI, 9:1 THF/H_2O (0.5 mL) was used as the solvent, KOH (5.6 mg, 0.1 mmol, 10 mol%) was used as the base, [Ru(*p*-cymene)Cl_2]$_2$ (15 mg, 0.025 mmol, 5 mol%) was used as the catalyst, (*S,S*)-TsDpen (18 mg, 0.05 mmol, 5 mol%) was used as the ligand, 1,4-butanediol (45 μL, 0.5 mmol) and γ-butyrolactone (38 μL, 0.5 mmol) were added and the reaction was performed at 30 ˚C and stirred for 1 hour. The ^{1}H NMR analysis was consistent with **3.1**.

Increasing amount of KOH

(Chapter 3, Section 3.2)

Following representative procedure XI, 9:1 THF/H_2O (0.5 mL) was used as the solvent, KOH (62 mg, 1.1 mmol, 1.1 eq.) was used as the base, [Ru(*p*-cymene)Cl_2]$_2$ (15

mg, 0.025 mmol, 5 mol%) was used as the catalyst, (*S,S*)-TsDpen (18 mg, 0.05 mmol, 5 mol%) was used as the ligand, 1,4-butanediol (45 μL, 0.5 mmol) was added and the reaction was performed at 30 ˚C and stirred for 1 hour. The ^{1}H NMR analysis was consistent with **3.1**.

Changing the ligand

(Table 3.8, Chapter 3, Section 3.2)

Following representative procedure XI, 9:1 THF/H_2O (0.5 mL) was used as the solvent, KOH (62 mg, 1.1 mmol, 1.1 eq.) was used as the base, [Ru(*p*-cymene)Cl_2]$_2$ (15 mg, 0.025 mmol, 5 mol%) was used as the catalyst, the appropriate ligand was used according to Table 3.8, 1,4-butanediol (45 μL, 0.5 mmol) was added and the reaction was performed at 30 ˚C and stirred for 1 hour. The ^{1}H NMR analysis was consistent with **3.1**.

Increasing amount of KOH

(Table 3.9, Chapter 3, Section 3.2)

Following representative procedure XI, 9:1 THF/H_2O (0.5 mL) was used as the solvent, the appropriate amount of KOH was used as the base according to Table 3.9, [Ru(*p*-cymene)Cl_2]$_2$ (15 mg, 0.025 mmol, 5 mol%) was used as the catalyst, (*1S,2R*)-(-)-*cis*-1-amino-2-indanol (22 mg, 0.15 mmol, 15 mol%) was used as the ligand, 1,4-butanediol (45 μL, 0.5 mmol) was added and the reaction was performed at 30 ˚C and stirred for 1 hour. The ^{1}H NMR analysis was consistent with **3.1**.

Increasing temperature

(Chapter 3, Section 3.2)

Following representative procedure XI, 9:1 THF/H_2O (0.5 mL) was used as the solvent, KOH (62 mg, 1.1 mmol, 1.1 eq.) was used as the base, [Ru(*p*-cymene)Cl_2]$_2$ (15 mg, 0.025 mmol, 5 mol%) was used as the catalyst, (*1S,2R*)-(-)-*cis*-1-amino-2-indanol (22 mg, 0.15 mmol, 15 mol%) was used as the ligand, 1,4-butanediol (90 μL, 1 mmol) was added and the reaction was performed at 50 ˚C and stirred for 1 hour. The ^{1}H NMR analysis was consistent with **3.1**.

Increasing amount of KOH

(Scheme 3.6, Chapter 3, Section 3.2)

Following representative procedure XI, 9:1 THF/H_2O (0.5 mL) was used as the solvent, KOH (62 mg, 1.1 mmol, 1.1 eq.) was used as the base, [Ru(*p*-cymene)Cl_2]$_2$ (15 mg, 0.025 mmol, 5 mol%) was used as the catalyst, the appropriate amount of (*1S,2R*)-(-)-*cis*-1-amino-2-indanol was used as the ligand according to Scheme 3.6, 1,4-butanediol (90 μL, 1 mmol) was added and the reaction was performed at 30 ˚C and stirred for 1 hour. The ^{1}H NMR analysis was consistent with **3.1**.

Varying the amount of ligand

(Table 3.10, Chapter 3, Section 3.2)

Following representative procedure XI, no solvent was used, KOH (62 mg, 1.1 mmol, 1.1 eq.) was used as the base, [Ru(*p*-cymene)Cl_2]$_2$ (15 mg, 0.025 mmol, 5 mol%) was used as the catalyst, the appropriate amount of (*1S,2R*)-(-)-*cis*-1-amino-2-indanol was used as the ligand according to Table 3.10, 1,4-butanediol (98 μL, 1.1 mmol, 1.1 eq.) was added and the reaction was performed at 50 ˚C and stirred for 1 hour. The ^{1}H NMR analysis was consistent with **3.1**.

(*S,S*)-TsDpen as the ligand

(Scheme 3.7, Chapter 3, Section 3.2)

Following representative procedure XI, the appropriate solvent was used according to Scheme 3.7, KOH (62 mg, 1.1 mmol, 1.1 eq.) was used as the base, [Ru(*p*-cymene)Cl_2]$_2$ (15 mg, 0.025 mmol, 5 mol%) was used as the catalyst, (*S,S*)-TsDpen (23 mg, 0.0625 mmol, 6.25 mol%) was used as the ligand, 1,4-butanediol (98 μL, 1.1 mmol, 1.1 eq.) was added and the reaction was performed at 50 ˚C and stirred for 1 hour. The ^{1}H NMR and HPLC analysis were consistent with **3.1**.

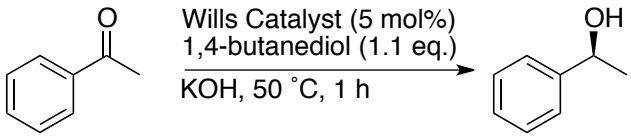
Changing the catalyst

(Table 3.11, Chapter 3, Section 3.3)

Following representative procedure XI, 9:1 THF/H_2O (0.5 mL) was used as the solvent, KOH (5.6 mg, 0.1 mmol, 10 mol%) was used as the base, the appropriate catalyst was used according to Table 3.11, (*S,S*)-TsDpen (18 mg, 0.05 mmol, 5 mol%) was used as the ligand, 1,4-butanediol (45 μL, 0.5 mmol) was added and the reaction was performed at 30 ˚C and stirred for 1 hour. The ^{1}H NMR and HPLC analysis were consistent with **3.1**.

Wills catalyst

Representative Procedure XII



To oven dried Youngs carousel tubes, KOH and (*S,S*)-teth-TsDpenRuCl (31 mg, 0.05 mmol, 5 mol%) were added and purged under argon for 10 minutes. The appropriate hydrogen acceptor, anhydrous solvent and acetophenone (117 μL, 1.0 mmol) were added to the solution using a micropipette. The tube was then sealed and the reaction mixture was immediately heated or cooled to the appropriate temperature and stirred for the appropriate amount of time. The resulting reaction mixture was then cooled or warmed to room temperature and extracted with DCM and water. The organic components were then dried and concentrated *in vacuo*. The resulting crude products were analyzed by their ^{1}H NMR spectra and then purified by column chromatography and enantiomeric excesses determined by HPLC analysis (Daicel Chiracel OD, 10% *i*-PrOH/hexane, 0.5 mL/min).

Amount of KOH

(Table 3.12, Chapter 3, Section 3.3)

Following representative procedure XII, no solvent was used, the appropriate amount of KOH was used according to Table 3.12, 1,4-butanediol (98 μL, 1.1 mmol, 1.1 eq.) was added as the hydrogen acceptor and the reaction was performed at 50 ˚C and stirred for 1 hour. The ^{1}H NMR and HPLC analysis were consistent with **3.1**.

THF as solvent

(Table 3.13, Chapter 3, Section 3.3)

Following representative procedure XII, the appropriate amount of 9:1 THF/H_2O was used as the solvent according to Table 3.13, KOH (5.6 mg, 0.1 mmol, 10 mol%) was used as the base, 1,4-butanediol (98 μL, 1.1 mmol, 1.1 eq.) was added as the hydrogen acceptor and the reaction was performed at 30 ˚C and stirred for 1 hour. The ^{1}H NMR and HPLC analysis were consistent with **3.1**.

Varying the amount of 1,4-butanediol

(Table 3.14, Chapter 3, Section 3.3)

Following representative procedure XII, no solvent was used, KOH (5.6 mg, 0.1 mmol, 10 mol%) was used as the base, the appropriate amount of 1,4-butanediol was added according to Table 3.14 as the hydrogen acceptor and the reaction was performed at 0 ˚C in an ice/water bath and stirred for 4 hours. The ^{1}H NMR and HPLC analysis were consistent with **3.1**.

***cis*-1,4-Butenediol as the hydrogen acceptor**

(Scheme 3.11, Chapter 3, Section 3.4)

Following representative procedure XII, no solvent was used, KOH (5.6 mg, 0.1 mmol, 10 mol%) was used as the base, *cis*-1,4-butenediol (82 μL, 1.0 mmol, 1.0 eq.) was added as the hydrogen acceptor and the reaction was performed at 0 ˚C in an ice/water bath and stirred for 4 hours. The ^{1}H NMR and HPLC analysis were consistent with **3.1**.

Lowering the temperature with *cis*-1,4-butenediol

(Scheme 3.12, Chapter 3, Section 3.4)

Following representative procedure XII, no solvent was used, KOH (5.6 mg, 0.1 mmol, 10 mol%) was used as the base, *cis*-1,4-butenediol (82 μL, 1.0 mmol, 1.0 eq.) was added as the hydrogen acceptor and the reaction was performed at -10 ˚C, maintained using an ice/KCl water bath and stirred for 4 hours. The ^{1}H NMR and HPLC analysis were consistent with **3.1**.

Racemization of (*S*)-1-phenylethanol

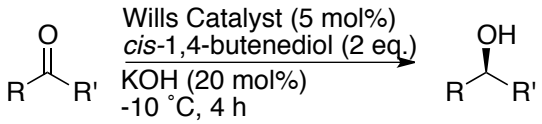
(Scheme 3.12, Chapter 3, Section 3.4)

Following representative procedure XII, no solvent was used, KOH (5.6 mg, 0.1 mmol, 10 mol%) was used as the base, *cis*-1,4-butenediol (82 μL, 1.0 mmol, 1.0 eq.) was added as the hydrogen acceptor, (*S*)-1-phenylethanol (121 μL, 1.0 mmol) was used in place of acetophenone and the reaction was performed at -10 ˚C, maintained using an ice/KCl water bath and stirred for 4 hours. The ^{1}H NMR and HPLC analysis were consistent with **3.1**.

Substrate scope

Representative Procedure XIII

(Table 3.15, Chapter 3, Section 3.4)



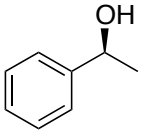
To oven dried Youngs carousel tubes, KOH (11.2 mg, 0.2 mmol, 20 mol%) and (*S*,*S*)-teth-TsDpenRuCl (31 mg, 0.05 mmol, 5 mol%) were added, purged under argon for 10 minutes and cooled to -10 ˚C in an ice/KCl water bath. The reagents were dissolved in THF (0.25 mL). *cis*-1,4-butenediol (164 μL, 2.0 mmol) and the appropriate ketone according to Table 3.15 were added to the solution using a micropipette. The tube was then sealed and the reaction mixture was stirred for 4 hours. The resulting reaction mixture was then cooled to room temperature and extracted with DCM and water. The organic components were then dried and concentrated *in vacuo*. The resulting crude products were purified by column chromatography. The products were analysed by their ^{1}H and ^{13}C NMR spectra and mass spectrometry data and enantiomeric excesses determined by HPLC analysis.

Synthesis of racemic alcohols for HPLC comparison

To oven dried Radleys carousel tubes, the appropriate ketone was added and dissolved in ethanol (1 mL). The mixture was cooled to 0 ˚C and $NaBH_4$ (18.9 mg, 0.5 mmol) was added carefully. The tube was then sealed and the reaction mixture was allowed to warm to room temperature and then heated to 80 ˚C and stirred for 2

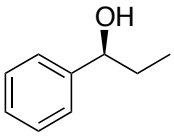
hours. The resulting reaction mixture was then cooled to room temperature and quenched with acetone (10 mL) and subsequently extracted with Et_2O and water. The organic components were then dried and concentrated *in vacuo*. The resulting crude products were purified by column chromatography where appropriate. The products were analysed by their ^1H and ^{13}C NMR spectra and mass spectrometry data and by HPLC analysis.

3.1 - (*S*)-1-Phenylethanol[147]



Following representative procedure XIII, acetophenone (117 μL, 1 mmol) was used as the ketone. The title compound was recovered as a colourless oil (104 mg, 83% yield) after column chromatography eluting with 9:1 Et_2O/hexane. ^1H NMR: ($CDCl_3$, 300 MHz) δ 7.47-7.24 (5H, m, Ar), 4.91 (1H, q, *J* = 6.4 Hz, CHOH), 1.51 (3H, d, *J* = 6.4 Hz, CH_3). ^{13}C NMR: ($CDCl_3$, 75.5 MHz) δ 145.8, 128.5, 127.5, 125.4, 70.5, 25.2. IR (film, cm^{-1}): ν_{max} = 3338, 2970, 1467, 1379, 1305, 1160, 1128, 951, 817, 699. ESI-MS of [C_8H_9O]; theoretical m/z of $[M+Na]^+$ = 145.0624, measured m/z of $[M+Na]^+$ = 145.0649. HPLC analysis: Daicel Chiracel OD, 10% *i*-PrOH/hexane, 0.5 mL/min; t_R 10.40 R, 12.94 S, >99% e.e.

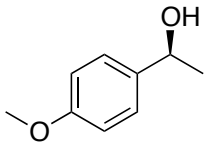
3.7 - (*S*)-1-Phenylpropan-1-ol[148]



Following representative procedure XIII, propiophenone (133 μL, 1 mmol) was used as the ketone species. The title compound was recovered as a colourless oil (69.5 mg, 51% yield) after column chromatography eluting with 9:1 Et_2O/hexane. ^1H NMR: ($CDCl_3$, 300 MHz) δ 7.49-7.19 (5H, m, Ar), 4.61 (1H, td, *J* = 6.8, 2.8 Hz, CHOH), 1.94-1.65 (2H, m, CH_2), 0.92 (3H, t, *J* = 7.4 Hz, CH_3). ^{13}C NMR: ($CDCl_3$, 75.5 MHz) δ 144.6, 128.4, 127.5, 126.0, 76.1, 31.9, 10.2. IR (film, cm^{-1}): ν_{max} = 3335, 2970, 1467, 1379, 1306, 1160, 1128, 951, 817, 670. ESI-MS of [$C_9H_{12}O$]; theoretical m/z of $[M+Na]^+$ =

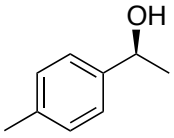
159.0780, measured m/z of $[M+Na]^+$ = 159.0795. HPLC analysis: Daicel Chiracel OD, 1% *i*-PrOH/hexane, 1.0 mL/min; t_R 22.18 R, 27.45 S, 96% e.e.

3.8 - (*S*)-1-(4-Methoxyphenyl)ethanol[147]



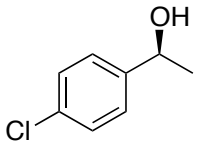
Following representative procedure XIII, 4-methoxyacetophenone (150 mg, 1 mmol) was used as the ketone. The title compound was recovered as a brown oil (151 mg, 99% yield) after column chromatography eluting with 9:1 Et_2O/hexane. ^1H NMR: ($CDCl_3$, 300 MHz) δ 7.24 (2H, d, *J* = 8.5 Hz, Ar), 6.82 (2H, d, *J* = 8.8 Hz, Ar), 4.80 (1H, qd, *J* = 6.3, 2.3 Hz, CHOH), 1.42 (3H, d, *J* = 6.4 Hz, CH_3). ^{13}C NMR: ($CDCl_3$, 75.5 MHz) δ 138.0, 126.7, 113.9, 70.0, 55.3, 53.4, 29.3, 25.1. IR (film, cm^{-1}): ν_{max} = 3375, 2970, 1360, 1257, 1172, 1029, 951, 833, 816. ESI-MS of $[C_9H_{12}O_2]$; theoretical m/z of $[M+Na]^+$ = 175.0730, measured m/z of $[M+Na]^+$ = 175.0690. HPLC analysis: Daicel Chiracel OD, 3% *i*-PrOH/hexane, 1.0 mL/min; t_R 18.29 R, 20.51 S, 96% e.e.

3.9 - (*S*)-1-(*p*-Tolyl)ethanol[148]



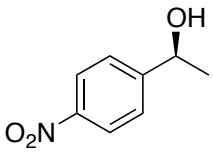
Following representative procedure XIII, 4-methylacetophenone (134 μL, 1 mmol) was used as the ketone. The title compound was recovered as a colourless oil (131 mg, 96% yield) after column chromatography eluting with 9:1 Et_2O/hexane. ^1H NMR: ($CDCl_3$, 300 MHz) δ 7.20 (2H, d, *J* = 7.5 Hz, Ar), 7.09 (2H, d, *J* = 7.9 Hz, Ar), 4.80 (1H, q, *J* = 6.4 Hz, CHOH), 2.27 (3H, s, Ar-CH_3) 1.42 (3H, d, *J* = 6.5 Hz, CH_3). ^{13}C NMR: ($CDCl_3$, 75.5 MHz) δ 142.9, 137.2, 129.2, 125.4, 70.3, 25.1, 21.1. IR (film, cm^{-1}): ν_{max} = 3338, 2970, 1467, 1379, 1307, 1160, 1128, 951, 817. ESI-MS of $[C_9H_{12}O]$; theoretical m/z of $[M+Na]^+$ = 159.0780, measured m/z of $[M+Na]^+$ = 159.0806. HPLC analysis: Daicel Chiracel OD, 10% *i*-PrOH/hexane, 0.5 mL/min; t_R 17.81 S, 18.93 R, >99% e.e.

3.10 - (*S*)-1-(4-Chlorophenyl)ethanol[148]



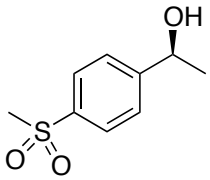
Following representative procedure XIII, 4-chloroacetophenone (130 μL, 1 mmol) was used as the ketone. The title compound was recovered as a colourless oil (146 mg, 93% yield) after column chromatography eluting with 9:1 Et_2O/hexane. ^1H NMR: ($CDCl_3$, 300 MHz) δ 7.31 (5H, s, Ar), 4.89 (1H, q, *J* = 6.4 Hz, CHOH), 1.48 (3H, d, *J* = 6.5 Hz, CH_3). ^{13}C NMR: ($CDCl_3$, 75.5 MHz) δ 144.3, 133.1, 128.6, 126.8, 69.8, 25.3. IR (film, cm^{-1}): ν_{max} = 3338, 2971, 1493, 1370, 1088, 1013, 950, 828, 778. ESI-MS of [$C_8H_9{}^{35}ClO$]; theoretical m/z of $[M-H]^-$ = 155.0269, measured m/z of $[M-H]^-$ = 155.0275. HPLC analysis: Daicel Chiracel OD, 5% *i*-PrOH/hexane, 0.5 mL/min; t_R 12.16 R, 13.16 S, >99% e.e.

3.11 - (*S*)-1-(4-Nitrophenyl)ethanol[148]



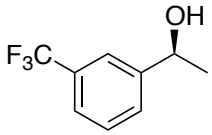
Following representative procedure XIII, 4-nitroacetophenone (165 mg, 1 mmol) was used as the ketone. The title compound was recovered as a yellow oil (92.3 mg, 55% yield) after column chromatography eluting with 9:1 Et_2O/hexane. ^1H NMR: ($CDCl_3$, 300 MHz) δ 8.21 (2H, d, *J* = 8.8 Hz, Ar), 7.55 (2H, d, *J* = 8.4 Hz, Ar), 5.03 (1H, qd, *J* = 6.4, 3.1 Hz, CHOH), 1.53 (3H, d, *J* = 6.5 Hz, CH_3). ^{13}C NMR: ($CDCl_3$, 75.5 MHz) δ 153.0, 126.1, 123.8, 77.2, 69.6, 25.6. IR (film, cm^{-1}): ν_{max} = 3346, 2973, 1517, 1343, 1089, 854, 699. ESI-MS of [$C_8H_9NO_3$]; theoretical m/z of $[M-H]^-$ = 166.0504, measured m/z of $[M-H]^-$ = 166.0502. HPLC analysis: Daicel Chiracel OB-H, 5% *i*-PrOH/hexane, 0.5 mL/min; t_R 42.80 S, 46.74 R, -26 (c = 1.0, $CHCl_3$), Lit value = -18, 86% e.e.

3.12 - (*S*)-1-(4-(Methylsulfonyl)phenyl)ethanol[149]



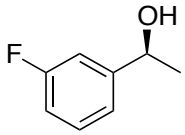
Following representative procedure XIII, 1-(4-(methylsulfonyl))ethanone (198 mg, 1 mmol) was used as the ketone. The title compound was recovered as a grey solid (181.5 mg, 91% yield) after column chromatography eluting with 9:1 Et_2O/hexane. ^1H NMR: ($CDCl_3$, 300 MHz) δ 7.83 (2H, d, *J* = 8.2 Hz, Ar), 7.51 (2H, d, *J* = 8.4 Hz), 4.94 (1H, q, *J* = 6.4 Hz, CHOH), 2.97 (3H, s, SO_2CH_3), 1.44 (3H, d, *J* = 6.5 Hz, CH_3). ^{13}C NMR: ($CDCl_3$, 75.5 MHz) δ 139.3, 127.6, 126.3, 69.6, 44.6, 25.5. IR (film, cm^{-1}): ν_{max} = 3469, 3007, 2975, 2921, 1410, 1277, 1144, 1089, 973, 833, 783, 761, 720, 652. ESI-MS of [$C_9H_{12}O_2$]; theoretical m/z of $[M+Na]^+$ = 223.0399, measured m/z of $[M+Na]^+$ = 223.0415. Enantiomeric excess determined by lanthanide shift reagent in ^1H NMR, Europium tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorate] (2 mg), 75% e.e. based on ^1H NMR data.

3.13 - (*S*)-1-(3-Trifluoromethylphenyl)ethanol[150]



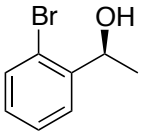
Following representative procedure XIII, 3-trifluoromethylacetophenone (152 μL, 1 mmol) was used as the ketone. The title compound was recovered as a colourless oil (112 mg, 59% yield) after column chromatography eluting with 9:1 Et_2O/hexane. ^1H NMR: ($CDCl_3$, 300 MHz) δ 7.58 (1H, s, Ar), 7.44 (dt, *J* = 24.6, 7.6 Hz, Ar), 4.91 (1H, q, *J* = 6.4 Hz, CHOH), 1.45 (3H, d, *J* = 6.5 Hz, CH_3). ^{13}C NMR: ($CDCl_3$, 75.5 MHz) δ 146.7, 129.0, 128.8, 124.2 (q, *J* = 4.0 Hz), 124.0 (q, *J* = 275 Hz), 121.4 (q, *J* = 3.9 Hz), 69.9, 25.4. ^{19}F NMR: (376 MHz, $CDCl_3$) δ -62.5. IR (film, cm^{-1}): ν_{max} = 3337, 2972, 1328, 1163, 1125, 1072, 950, 803, 703. ESI-MS of [$C_9H_9F_3O$]; theoretical m/z of $[M-H]^-$ = 189.0533, measured m/z of $[M-H]^-$ = 189.0516. [α]$_D^{20}$: -26 (c = 1.0, $CHCl_3$), Lit value = -27.9(c = 1.0, $CHCl_3$), 93% e.e. based on rotation.

3.14 - (*S*)-1-(3-Fluorophenyl)ethanol[151]



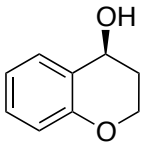
Following representative procedure XIII, 3-fluoroacetophenone (123 μL, 1 mmol) was used as the ketone. The title compound was recovered as a colourless oil (116 mg, 83% yield) after column chromatography eluting with 9:1 Et_2O/hexane. ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 7.27-7.20 (1H, m, Ar), 7.07-7.01 (2H, m, Ar), 6.92-6.85 (1H, m, Ar), 4.83 (1H, q, *J* = 6.4 Hz, CHOH), 1.42 (3H, d, *J* = 6.5 Hz, CH_3). ^{13}C NMR: ($CDCl_3$, 75.5 MHz) δ 163.0 (d, *J* = 245.7 Hz), 148.5 (d, *J* = 6.4 Hz), 130.0 (d, *J* = 8.1 Hz), 120.9 (d, *J* = 2.9 Hz), 114.3 (d, *J* = 21.2 Hz), 112.2 (d, *J* = 21.8 Hz), 69.8 (d, *J* = 1.8 Hz), 25.3. ^{19}F NMR: (376 MHz, $CDCl_3$) δ -112.9. IR (film, cm^{-1}): ν_{max} = 3344, 2971, 1466, 1379, 1305, 1161, 1128, 950, 817, 696. ESI-MS of [C_8H_9OF]; theoretical m/z of $[M+Na]^+$ = 163.0530, measured m/z of $[M+Na]^+$ = 163.0564. [α]$_D^{20}$: -32 (c = 1.0, $CHCl_3$), Lit value – 39.8 (c = 1.8, $CHCl_3$), 80% e.e. based on rotation.

3.15 - (*S*)-1-(2-Bromophenyl)ethanol[147]



Following representative procedure XIII, 2-Bromoacetophenone (135 μL, 1 mmol) was used as the ketone. The title compound was recovered as a colourless oil (179 mg, 89% yield) after column chromatography eluting with 9:1 Et_2O/hexane. ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 7.60 (1H, dd, *J* = 7.8, 1.7 Hz, Ar), 7.52 (1H, dd, *J* = 8.0, 1.2 Hz), 7.35 (1H, td, *J* = 7.7, 1.1 Hz), 7.17-7.08 (1H, m), 5.25 (1H, q, *J* = 6.3 Hz, CHOH), 1.49 (3H, d, *J* = 6.4 Hz, CH_3). ^{13}C NMR: ($CDCl_3$, 75.5 MHz) δ 144.6, 132.7, 128.8, 127.9, 126.7, 121.8, 69.2, 23.6. IR (film, cm^{-1}): ν_{max} = 3320, 2972, 1440, 1368, 1127, 1091, 1024, 948, 899, 751, 667. ESI-MS of [$C_8H_9{}^{79}BrO$]; theoretical m/z of $[M+Na]^+$ = 222.9729, measured m/z of $[M+Na]^+$ = 222.9716. HPLC analysis: Daicel Chiracel OD, 2% *i*-PrOH/hexane, 1.0 mL/min; t_R 8.79 S, 10.23 R, 79% e.e.

3.16 - (*S*)-Chroman-4-ol[147]



Following representative procedure XIII, 4-chromanone (148 mg, 1 mmol) was used as the ketone. The title compound was recovered as a white solid (120.4 mg, 80% yield) after column chromatography eluting with 9:1 Et_2O/hexane. ^1H NMR: ($CDCl_3$, 300 MHz) δ 7.26-7.11 (2H, m, Ar), 6.88-6.76 (2H, m, Ar), 4.72-4.71 (1H, m, CHOH), 4.22-4.18 (2H, m, $CHOHCH_2$), 2.11-1.90 (2H, m, $CHOHCH_2CH_2$). ^{13}C NMR: ($CDCl_3$, 75.5 MHz) δ 160.2, 154.6, 129.8, 129.7, 124.3, 120.6, 117.1, 63.3, 61.9, 30.8. IR (film, cm^{-1}): ν_{max} = 3337, 2970, 1489, 1379, 1127, 1066, 950, 816, 754. ESI-MS of [$C_9H_{10}O_2$]; theoretical m/z of $[M+Na]^+$ = 173.0573, measured m/z of $[M+H]^+$ = 173.0588. HPLC analysis: Daicel Chiracel OD, 5% *i*-PrOH/hexane, 1.0 mL/min; t_R 23.46 R, 30.19 S, >99% e.e.

***cis*-1,4-Butenediol with untethered catalyst**

(Table 3.16, Chapter 3, Section 3.5)

Following representative procedure XI, THF (0.25 mL) was used as the solvent, KOH (5.6 mg, 0.1 mmol, 10 mol%) was used as the base, $[Ru(p\text{-cymene})Cl_2]_2$ (15 mg, 0.025 mmol, 5 mol%) was used as the catalyst, (*S,S*)-TsDpen (23 mg, 0.0625 mmol, 6.25 mol%) was used as the ligand, the appropriate amount of *cis*-1,4-butenediol was used according to Table 3.16 instead of 1,4-butanediol and the reaction was performed at 30 ˚C and stirred for 1 hour. The ^1H NMR analysis was consistent with **3.1**.

Slow addition

(Scheme 3.13, Chapter 3, Section 3.5)

Following representative procedure XI, THF (0.25 mL) was used as the solvent, KOH (5.6 mg, 0.1 mmol, 10 mol%) was used as the base, $[Ru(p\text{-cymene})Cl_2]_2$ (15 mg, 0.025 mmol, 5 mol%) was used as the catalyst, (*S,S*)-TsDpen (23 mg, 0.0625 mmol, 6.25 mol%) was used as the ligand, *cis*-1,4-butenediol (82 μL, 1.0 mmol) was added to the solution using a micropipette every 30 minutes instead of 1,4-butanediol and the

reaction was performed at 30 ˚C and stirred for 2 hours. The ^{1}H NMR and HPLC analysis were consistent with **3.1**.

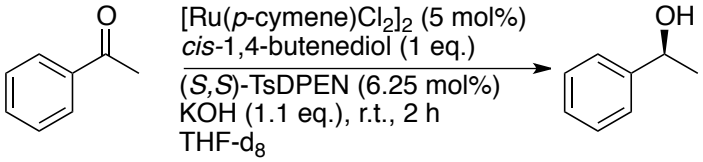
Increasing catalyst loading

(Scheme 3.14, Chapter 3, Section 3.5)

Following representative procedure XI, THF (0.25 mL) was used as the solvent, KOH (62 mg, 1.1 mmol, 1.1 eq.) was used as the base, [Ru(*p*-cymene)Cl_2]$_2$ (30 mg, 0.05 mmol, 10 mol%) was used as the catalyst, (*S,S*)-TsDpen (46 mg, 0.125 mmol, 12.5 mol%) was used as the ligand, *cis*-1,4-butenediol (82 μL, 1.0 mmol) was added to the solution using a micropipette every 30 minutes instead of 1,4-butanediol and the reaction was performed at 30 ˚C and stirred for 2 hours. The ^{1}H NMR and HPLC analysis were consistent with **3.1**.

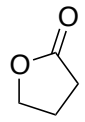
Mechanistic investigation

Representative Procedure XIV



To an oven dried NMR tube the KOH (62 mg, 1.1 mmol, 1.1 eq.), [Ru(*p*-cymene)Cl_2]$_2$ (15 mg, 0.025 mmol, 5 mol%), (*S,S*)-TsDpen (23 mg, 0.0625 mmol, 6.25 mol%) were added and purged under argon for 10 minutes. THF-d_8 (1 mL) dissolved the reagents, *cis*-1,4-butenediol (82 μL, 1.0 mmol) and acetophenone (117 μL, 1.0 mmol) were added to the solution using a micropipette. The tube was then sealed and the reaction mixture was immediately placed in the pre-heated NMR machine at 30 ˚C. ^{1}H NMR spectra were then taken every 2 minutes over 30 minutes. ^{1}H NMR spectra confirmed the formation of a small amount of **3.6** by comparison of the peaks at 4.31 (2H, t, *J* = 7.0 Hz, CH_2, **3.6**) and 5.75 (2H, m, HC=CH, *cis*-1,4-butenediol). Over the 30 minute experiment *cis*-1,4-butenediol disappears and 1,4-butanediol appears by comparison of the peaks at 3.73-3.64 (2H, m, CH_2, 1,4-butanediol) and 5.75 (2H, m, HC=CH, *cis*-1,4-butenediol).

3.6 - γ-Butyrolactone

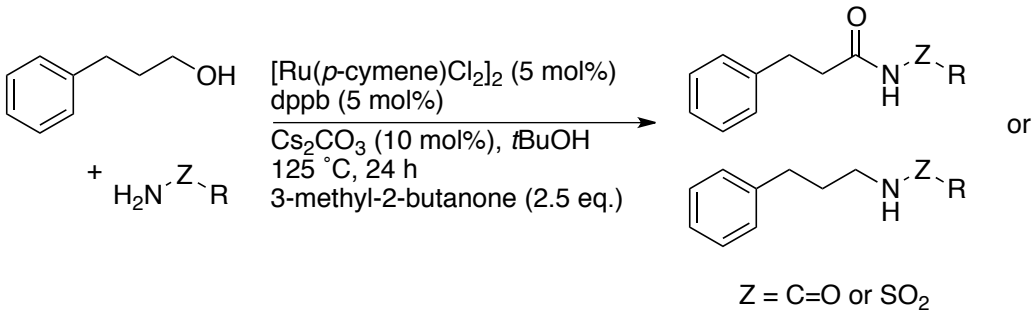


^{1}H NMR: (Acetone-d_6, 400 MHz) δ 4.31 (2H, t, *J* = 7.0 Hz, CH_2), 2.44 (2H, t, *J* = 8.0 Hz, CH_2), 2.25 (2H, p, *J* = 7.7, 7.9 Hz, CH_2).

5.4 Chapter 4 Experimental Methods

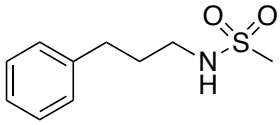
Representative Procedure XV

(Table 4.1, Chapter 4, Section 4.2)



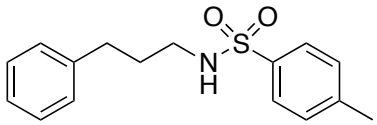
To oven dried Youngs carousel tubes, Cs_2CO_3 (98 mg, 0.3 mmol, 10 mol%), [Ru(*p*-cymene)Cl_2]$_2$ (46 mg, 0.075 mmol, 5 mol%), dppb (64 mg, 0.15 mmol, 5 mol%) and the appropriate sulfonamide or amide according to Table 4.1 were added and purged under argon for 10 minutes. *t*BuOH (3 mL) dissolved the reagents, the appropriate hydrogen acceptor and the appropriate alcohol were added to the solution using a micropipette. The tube was then sealed and the reaction mixture was immediately heated to 125 ˚C and stirred for 24 hours. The resulting reaction mixture was then cooled to room temperature and extracted with DCM and water. The organic components were then dried and concentrated *in vacuo*. The resulting crude products were analyzed by their ^{1}H NMR spectra.

4.1 - *N*-(3-Phenylpropyl)-methanesulfonamide[152]



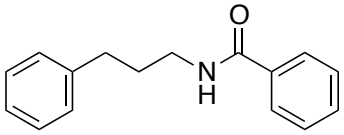
Following representative procedure XV, methanesulfonamide (0.317 g, 3.33 mmol, 1.1 eq.) was used as the sulfonamide species, 3-phenyl-1-propanol (409 μL, 3.0 mmol) was used as the alcohol and 3-methyl-2-butanone (0.8 mL, 7.5 mmol, 2.5 eq.) was used as the hydrogen acceptor. ^{1}H NMR of the crude product showed a 43% conversion into **4.1** by comparison of the peaks at 3.13 (3H, s, CH_3 methansulfonamide) and 2.97 (3H, s, CH_3, **4.1**). ^{1}H NMR: ($CDCl_3$, 250 MHz) δ 7.36-7.15 (5H, m, Ar), 4.41 (1H, br.s, NH), 3.25-3.14 (2H, m, CH_2), 2.97 (3H, s, CH_3), 2.81-2.65 (2H, m, CH_2), 2.02-1.85 (2H, m, CH_2). ESI-MS of [$C_{10}H_{15}NO_2S$]; theoretical m/z of $[M+Na]^+$ = 236.1508, measured m/z of $[M+Na]^+$ = 236.1503.

4.2 - *N*-(3-Phenylpropyl)-methanesulfonamide[152]



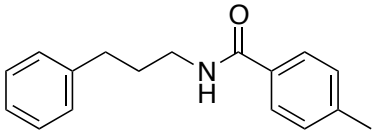
Following representative procedure XV, *p*-toluenesulfonamide (0.570 g, 3.33 mmol, 1.1 eq.) was used as the sulfonamide species, 3-phenyl-1-propanol (409 μL, 3.0 mmol) was used as the alcohol and 3-methyl-2-butanone (0.8 mL, 7.5 mmol, 2.5 eq.) was used as the hydrogen acceptor. ^{1}H NMR of the crude product showed a 79% conversion into **4.2** by comparison of the peaks at 3.71 (2H, t, *J* = 6.4 Hz, CH_2, 3-phenylpropan-1-ol) and 3.06-2.91 (2H, m, CH_2, **4.2**). ^{1}H NMR: ($CDCl_3$, 250 MHz) δ 7.76 (2H, d, *J* = 8.2 Hz, Ar), 7.36-7.05 (7H, m, Ar), 4.98 (1H, br.s, NH), 3.06-2.91 (2H, m, CH_2), 2.70-2.56 (2H, m, CH_2), 2.46 (3H, s, CH_3), 1.87-1.73 (2H, m, CH_2). ESI-MS of [$C_{16}H_{19}NO_2S$]; theoretical m/z of $[M+H]^+$ = 290.1215, measured m/z of $[M+H]^+$ = 290.1207.

4.3 - *N*-(3-Phenylpropyl)-benzamide[153]



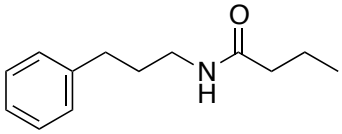
Following representative procedure XV, benzamide (403 g, 3.33 mmol, 1.1 eq.) was used as the amide species, 3-phenyl-1-propanol (409 μL, 3.0 mmol) was used as the alcohol and 3-methyl-2-butanone (0.8 mL, 7.5 mmol, 2.5 eq.) was used as the hydrogen acceptor. ^{1}H NMR of the crude product showed a 29% conversion into **4.3** by comparison of the peaks at 3.71 (2H, t, *J* = 6.4 Hz, CH_2, 3-phenylpropan-1-ol) and 3.65-3.62 (2H, m, CH_2, **4.3**). ^{1}H NMR: ($CDCl_3$, 250 MHz) δ 7.70 (2H, d, *J* = 7.4 Hz), 7.61-7.11 (8H, m, Ar), 6.19 (1H, br.s, NH), 3.65-3.62 (2H, m, CH_2), 2.67-2.54 (2H, m, CH_2), 1.99-1.83 (2H, m, CH_2). ESI-MS of [$C_{16}H_{17}NO$]; theoretical m/z of $[M+NA]^+$ = 262.1208, measured m/z of $[M+Na]^+$ = 262.1191.

4.4 - 4-Methyl-*N*-(3-phenylpropyl)benzamide



Following representative procedure XV, 4-methylbenzamide (450 mg, 3.33 mmol, 1.1 eq.) was used as the amide species, 3-phenyl-1-propanol (409 μL, 3.0 mmol) was used as the alcohol and 3-methyl-2-butanone (0.8 mL, 7.5 mmol, 2.5 eq.) was used as the hydrogen acceptor. The ^{1}H NMR: ($CDCl_3$, 250 MHz) of the crude product showed a 6% conversion into **4.4** by comparison of the peaks at 3.71 (2H, t, *J* = 6.4 Hz, CH_2, 3-phenylpropan-1-ol) and 3.55-3.44 (2H, m, CH_2, **4.4**). ESI-MS of [$C_{17}H_{19}NO$]; theoretical m/z of $[M+H]^+$ = 254.1545, measured m/z of $[M+H]^+$ = 254.1540.

4.5 - *N*-(3-Phenylpropyl)-butyramide[154]



Following representative procedure XV, butyramide (290 mg, 3.33 mmol, 1.1 eq.) was used as the amide species, 3-phenyl-1-propanol (409 μL, 3.0 mmol) was used as

the alcohol and 3-methyl-2-butanone (0.8 mL, 7.5 mmol, 2.5 eq.) was used as the hydrogen acceptor. The ^{1}H NMR: ($CDCl_3$, 250 MHz) of the crude product showed a 19% conversion into **4.5** by comparison of the peaks at 3.71 (2H, t, *J* = 6.4 Hz, CH_2, 3-phenylpropan-1-ol) and 3.55-3.42 (2H, m, CH_2, **4.5**).

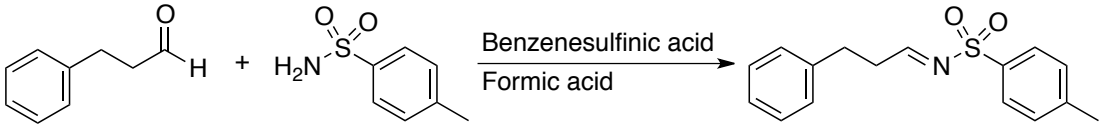
Varying hydrogen acceptor

(Table 4.2, Chapter 4, Section 4.2)

Following representative procedure XV, methanesulfonamide (317 mg, 3 mmol) was used as the sulfonamide species, 3-phenyl-1-propanol (409 μL, 3.0 mmol) was used as the alcohol and the appropriate hydrogen acceptor was added according to Table 4.2. The ^{1}H NMR: ($CDCl_3$, 250 MHz) of the crude reaction mixture showed % conversion by comparison of the peaks at 3.13 (3H, s, CH_3 methansulfonamide) and 2.97 (3H, s, CH_3, **4.1**).

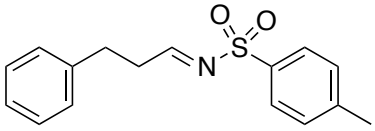
Synthesis of sulfonimine 4.6

(Chapter 4, Section 4.2)



To an oven dried flask, benzenesulfinic acid sodium salt (9.02 g, 55 mmol) and *p*-toluenesulfonamide (8.560 g, 50 mmol) were added. Formic acid 50% solution (100 mL) dissolved the reagents, hydrocinnamaldehyde (6.58 mL, 50 mmol) was added to the solution using a syringe. The reaction mixture was stirred for 18 hours at room temperature. The resulting reaction mixture was then diluted with H_2O (100 mL), filtered and washed with H_2O and hexane. The filter cake was dissolved in DCM (375 mL) and stirred with $NaHCO_3$ (saturated solution, 375 mL) for 2 hours. The reaction mixture was then extracted with DCM and water. The organic components were then dried and concentrated *in vacuo*. The product was analysed by its ^{1}H NMR and mass spectrometry data.

4.6 - 4-Methyl-*N*-(3-phenylpropylidene)benzenesulfonamide[155]



Compound **4.6** was isolated as a white solid (10.65 g, 74%). ^{1}H NMR: ($CDCl_3$, 250 MHz) δ 8.56 (1H, t, *J* = 4.0 Hz), 7.70 (2H, d, *J* = 8.4 Hz), 7.31-7.01 (7H, m), 2.96-2.83 (2H, m), 2.83-2.69 (2H, m), 2.38 (3H, s). ESI-MS of [$C_{16}H_{17}NO_2S$]; theoretical m/z of $[M+H]^+$ = 288.1058, measured m/z of $[M+H]^+$ = 288.1048.

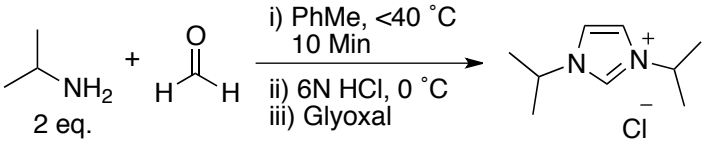
Using 4.6 as the hydrogen acceptor

(Scheme 4.5, Chapter 4, Section 4.2)

Following representative procedure XV, methanesulfonamide (317 mg, 3 mmol) was used as the sulfonamide species, benzyl alcohol (310 μL, 3.0 mmol) was used as the alcohol and sulfonimine **4.6** (2.155 g, 7.5 mmol, 2.5 eq.) was used as the hydrogen acceptor. The ^{1}H NMR: ($CDCl_3$, 250 MHz) of the crude reaction mixture showed % conversion by comparison of the peaks at 3.13 (3H, s, CH_3 methansulfonamide) and 2.97 (3H, s, CH_3, **4.7**).

Synthesis of NHC precursor 4.8[118]

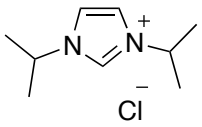
(Scheme 4.6, Chapter 4, Section 4.2)



To an oven dried flask, *iso*propylamine (3.09 mL, 30 mmol) was added dropwise to a suspension of paraformaldehyde (2.25 mL, 30 mmol) in toluene (10 mL) using a syringe. Ensuring the temperature was kept below 40 ˚C the mixture was stirred for 10 minutes. The mixture was then cooled to 0 ˚C in an ice/water bath and a second portion of *iso*propylamine (3.09 mL, 30 mmol) was added dropwise using a syringe, subsequently HCL (6 mL, 30 mmol, 6N) was added to the solution using a syringe. The reaction mixture was allowed to warm to room temperature and glyoxal (3.41 mL, 30 mmol) was added dropwise using a syringe. The resulting reaction mixture was then stirred overnight to give a brown solution. The reaction mixture was then

extracted with DCM and water. The organic components were then dried and concentrated *in vacuo*. The product was analysed by ^{1}H NMR.

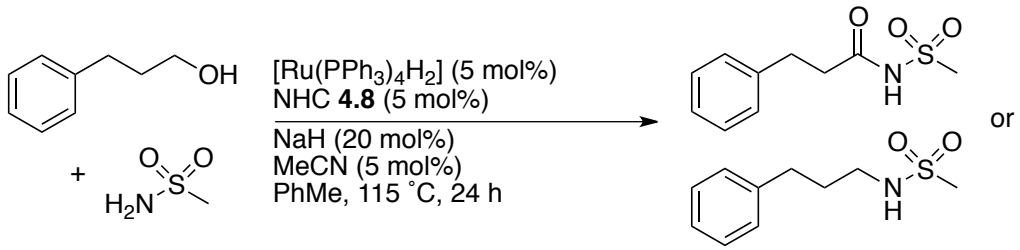
4.8 - 1,3-Diisopropyl-1*H*-imidazol-3-ium chloride[118]



Compound **4.8** was isolated as a brown oil (4.126 g, 73%). ^{1}H NMR: (D_2O, 250 MHz) δ 8.81-8.65 (1H, m, CH), 7.53-7.35 (1H, m, CH), 4.50 (2H, m, CH), 1.42 (12H, d, *J* = 8.1 Hz, CH_3).

Using NHC precursor

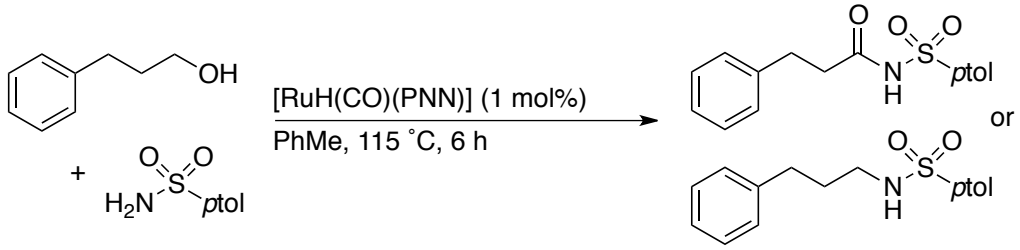
(Scheme 4.7, Chapter 4, Section 4.2)



To oven dried and degassed Youngs carousel tubes, NaH (2.4 mg, 0.1 mmol, 20 mol%), $RuH_2(PPh_3)_4$ (28 mg, 0.025 mmol, 5 mol%) and NHC precursor **4.8** (4.7 mg, 0.025 mmol, 5 mol%) were added under an inert atmosphere in a glovebox. Anhydrous toluene (0.5 mL) dissolved the reagents and anhydrous MeCN (1.2 μL, 0.025 mmol, 5 mol%) was added to the solution using a micropipette. The tube was then sealed and the reaction mixture was immediately heated to 115 ˚C and stirred for 1 hour. To the pre-reaction mixture methanesulfonamide (47.5 mg, 0.5 mmol) and 3-phenyl-1-propanol (68 μL, 0.5 mmol) were then added and the reaction mixture was stirred at 115 ˚C for 24 hours. The resulting reaction mixture was then cooled to room temperature and extracted with DCM and water. The organic components were then dried and concentrated *in vacuo*. The resulting crude products were analysed by their ^{1}H NMR spectra.

Using Milstein's catalyst[80]

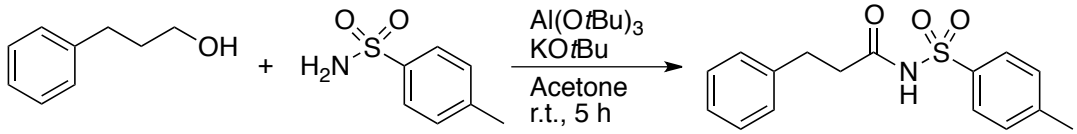
(Scheme 4.8, Chapter 4, Section 4.2)



To oven dried and degassed Youngs carousel tubes, RuH(CO)(PNN) (4.5 mg, 0.01 mmol, 1 mol%) and *p*-toluenesulfonamide (171 mg, 1 mmol) were added under an inert atmosphere of argon in a glovebox. Anhydrous toluene (3 mL) dissolved the reagents, 3-phenyl-1-propanol (136 μL, 1 mmol) was added to the solution using a micropipette. The tube was then sealed and the reaction mixture was immediately heated to 115 ˚C and stirred for 24 hours. The resulting reaction mixture was then cooled to room temperature and extracted with DCM and water. The organic components were then dried and concentrated *in vacuo*. The resulting crude products were analysed by their ^{1}H NMR spectra.

Representative Procedure XVI

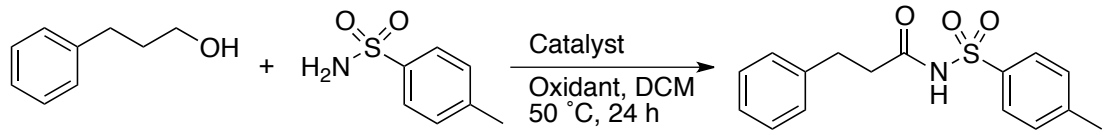
(Table 4.3, Chapter 4, Section 4.3)



To oven dried Radleys carousel tubes, the appropriate amount of KO*t*Bu and Al(O*t*Bu)$_3$ according to Table 4.3 and *p*-toluenesulfonamide (171 mg, 1 mmol) were added. Anhydrous acetone (3 mL) dissolved the reagents, 3-phenyl-1-propanol (136 μL, 1 mmol) was added to the solution using a micropipette. The tube was then sealed and the reaction mixture was stirred for 5 hours at room temperature. The resulting reaction mixture was then extracted with DCM and water. The organic components were then dried and concentrated *in vacuo*. The resulting crude products were analysed by their ^{1}H NMR spectra. The ^{1}H NMR: ($CDCl_3$, 250 MHz) of the crude reaction mixture showed no conversion into **2.27**.

Changing catalyst and oxidant

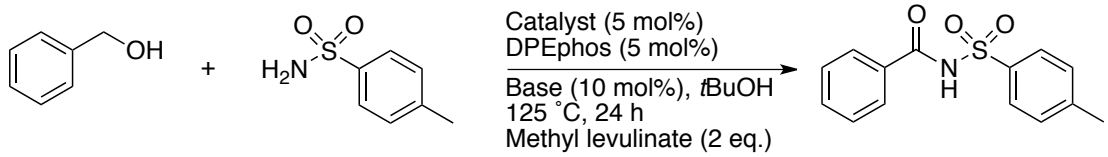
(Table 4.4, Chapter 4, Section 4.3)



To oven dried Radleys carousel tubes, the appropriate oxidant and catalyst according to Table 4.4 and *p*-toluenesulfonamide (171 mg, 1 mmol) were added. Anhydrous DCM (2 mL) dissolved the reagents, 3-phenyl-1-propanol (136 μL, 1 mmol) was added to the solution using a micropipette. The tube was then sealed and the reaction mixture was immediately heated to 50 ˚C and stirred for 24 hours. The resulting reaction mixture was cooled to room temperature and then extracted with DCM and water. The organic components were then dried and concentrated *in vacuo*. The resulting crude products were analysed by their ^{1}H NMR spectra. The ^{1}H NMR: ($CDCl_3$, 250 MHz) of the crude reaction mixture showed no conversion into **2.27**.

Using methyl levulinate as the hydrogen acceptor

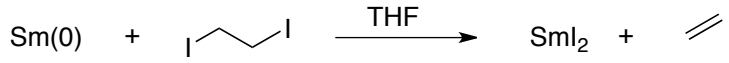
(Table 4.5, Chapter 4, Section 4.4)



To oven dried Youngs carousel tubes, the appropriate base (0.1 mmol, 10 mol%) and the appropriate catalyst (5 mol%) according to Table 4.5, DPEphos (27 mg, 0.05 mmol, 5 mol%) and *p*-toluenesulfonamide (171 mg, 1 mmol) were added and purged under argon for 10 minutes. *t*BuOH (1 mL) dissolved the reagents, methyl levulinate (248 μL, 2 mmol, 2 eq.) and benzyl alcohol (207 μL, 2.0 mmol, 2 eq.) were added to the solution using a micropipette. The tube was then sealed and the reaction mixture was immediately heated to 115 ˚C and stirred for 24 hours. The resulting reaction mixture was then cooled to room temperature and extracted with DCM and water. The organic components were then dried and concentrated *in vacuo*. The ^{1}H NMR: ($CDCl_3$, 250 MHz) of the crude reaction mixture showed no conversion into **2.23**.

Synthesis of SmI_2[121]

(Scheme 4.13, Chapter 4, Section 4.4)



To an oven dried and degassed Schlenk flask, diiodoethane (1.322 mL, 10 mmol) was dissolved in anhydrous THF (250 mL). Samarium metal (3.000 g, 20 mmol) was added under an inert atmosphere of argon. The flask was then sealed and the reaction mixture was stirred for 24 hours. The resulting solution was a characteristic deep blue colour. In order to maintain the freshness of the sample the excess Samarium metal was kept in the Schlenk flask and the solution was continuously stirred under an argon atmosphere. The resulting solution was SmI_2 (0.04 M in THF).

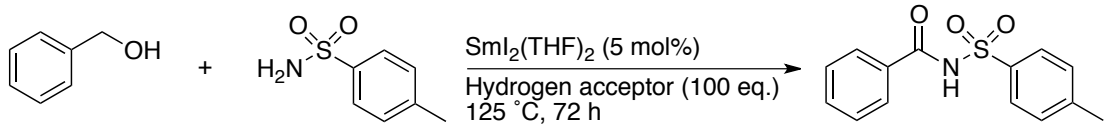
Preparation of $SmI_2(THF)_2$[122]

(Chapter 4, Section 4.4)

To an oven dried and degassed Schlenk flask, SmI_2 (1.25 mL, 0.05 mmol, 0.04 M) was added by using a syringe. The solvent was then removed *in vacuo*. The remaining dried compound was $SmI_2(THF)_2$ in accordance with the literature procedure.[122]

Using the $SmI_2(THF)_2$

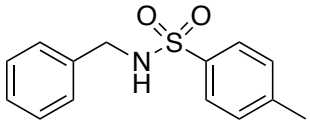
(Table 4.6, Chapter 4, Section 4.4)



To oven dried Youngs carousel tubes, SmI_2 (1.25 mL, 0.05 mmol, 0.04 M) was added by using a syringe. The solvent was then removed *in vacuo*. *p*-Toluenesulfonamide (171 mg, 1 mmol) was added and degassed. Anhydrous DCM (1 mL) dissolved the reagents, benzyl alcohol (104 μL, 1.0 mmol) and the appropriate hydrogen acceptor according to Table 4.6 were added to the solution using a micropipette or syringe as appropriate. The tube was then sealed and the reaction mixture was immediately heated to 125 ˚C and stirred for 72 hours. The resulting reaction mixture was then cooled to room temperature and extracted with DCM and water. The organic

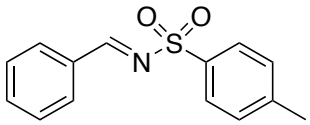
components were then dried and concentrated *in vacuo*. ^{1}H NMR: (DMSO, 250 MHz) of the crude reaction mixture showed no conversion into **2.23**.

4.12 - *N*-Benzyl-4-methylbenzensulfonamide[156]



^{1}H NMR: (DMSO, 250 MHz) of the crude reaction mixture showed no conversion into **4.12**.

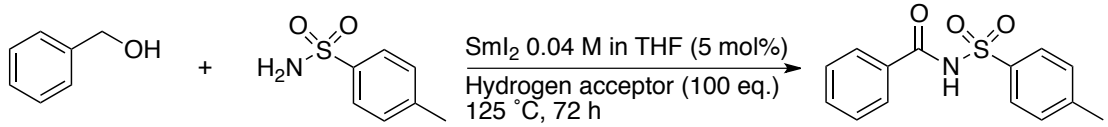
4.13 - *N*-Benzylidene-4-methylbenzensulfonamide[157]



^{1}H NMR: (DMSO, 250 MHz) of the crude reaction mixture showed % conversion by comparison of the peaks at 4.51 (2H, s, CH_2 benzyl alcohol) and 8.91 (1H, s, N=CH, **4.13**).

Using the SmI_2

(Table 4.6, Chapter 4, Section 4.4)

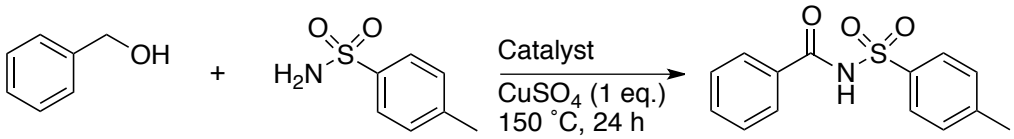


To oven dried Youngs carousel tubes, SmI_2 (1.25 mL, 0.05 mmol, 0.04 M) was added by using a syringe. *p*-Toluenesulfonamide (171 mg, 1 mmol) was added and degassed. Benzyl alcohol (207 μL, 2.0 mmol, 2 eq.) and the appropriate hydrogen acceptor according to Table 4.7 were added to the solution using a micropipette or syringe as appropriate. The tube was then sealed and the reaction mixture was immediately heated to 125 ˚C and stirred for 72 hours. The resulting reaction mixture was then cooled to room temperature and extracted with DCM and water. The organic components were then dried and concentrated *in vacuo*. ^{1}H NMR: (DMSO, 250 MHz) of the crude reaction mixture showed no conversion into **2.23**. ^{1}H NMR: (DMSO, 250 MHz) of the crude reaction mixture showed no conversion into

4.12. The ^{1}H NMR: (DMSO, 250 MHz) of the crude reaction mixture showed % conversion by comparison of the peaks at 4.51 (2H, s, CH_2 benzyl alcohol) and 8.91 (1H, s, N=CH, **4.13**).

Using $CuSO_4$ as an oxidant

(Table 4.8, Chapter 4, Section 4.4)



To oven dried Youngs carousel tubes, the appropriate catalyst according to Table 4.8, $CuSO_4$ (160 mg, 1 mmol, 1 eq.) and *p*-toluenesulfonamide (171 mg, 1 mmol) were added and purged under argon for 10 minutes. Benzyl alcohol (414 μL, 4.0 mmol, 4 eq.) was added to the solution using a micropipette. The tube was then sealed and the reaction mixture was immediately heated to 115 ˚C and stirred for 24 hours. The resulting reaction mixture was then cooled to room temperature and extracted with DCM and water. The organic components were then dried and concentrated *in vacuo*. ^{1}H NMR: ($CDCl_3$, 250 MHz) of the crude reaction mixture showed no conversion into **2.23**. The ^{1}H NMR: ($CDCl_3$, 250 MHz) of the crude reaction mixture showed % conversion by comparison of the peaks at 4.60 (2H, s, CH_2 benzyl alcohol) and 4.15 (2H, d, J = 6.2 Hz, CH_2, **4.12**). The ^{1}H NMR: ($CDCl_3$, 250 MHz) of the crude reaction mixture showed % conversion by comparison of the peaks at 4.60 (2H, s, CH_2 benzyl alcohol) and 9.06 (1H, s, N=CH, **4.13**).

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Chapter 6: References

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